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PHYSIOLOGY AS A GUIDE TO COMBATING TROPICAL STRESS*

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MAN is a tropical animal! Those who doubt it should ask themselves in what kind of climate man — naked, defenceless, fireless man — could possibly have evolved from his arboreal progenitors. In what kind of climate could he have dwelt in the trees? In what kind of climate could he have been free to roam, explore and investigate the new horizontal world; to exploit a patience for experimenting in the arts of fire making and fire controlling; and to develop the skills for skinning animals, salvaging the skins, assembling the pieces into a protective garment and fashioning attachments? Surely not in a world whose cold confined him to the neighborhood of sheltering caves for considerable periods!

What, then, has happened to man that makes the implication behind the title of this lecture admissible? What happened to make it appear reasonable to the Greeks that a zone of impenetrable heat lay to the South, which only a few Ethiopians, blackened beyond human semblance, had survived? What happened to create for some of us here present pictures of heroic empire builders, braving tropical rigors and carrying the white man's burden where the climate had sapped all virility from the suffering heathen?

What happened, of course, was that certain groups of primitive men, possessed of their new clothes, proud in their new accomplishments and subjected to some positive selection thereby, had spread into the more northerly temperate and cold temperate regions and had developed there certain cultures, practices and beliefs that they termed "civilization." Then, after the lapse of several thousand years, secure alike in ignorance of their origins and pride of their achievements, these northern men had rediscovered the tropical regions and had endeavored to apply to them the practices of their temperate culture. Those who returned to take up any period of residence in the tropics were constrained by pride, or by social pressure, to conduct themselves after the manner of their kind.

Thus arose a conflict between the nature of man and the nature of a culture that interfered with the acceptance of his physiologic birthright. It was in the interests of the social group that the superiority of the northern culture should be maintained at all possible points, and there were ready to hand two very good "explanations" of the difficulties encountered by its emissaries. The first was the widespread incidence of diseases unfamiliar at home (or at least in the more "advanced" of the home countries), and therefore characterized as "tropical." The second, in part responsible for the first, was the pitiful ignorance displayed by the indigenous peoples, which made them unappreciative of the superiority of the northern way of life.

Time, experience and a certain mellowing of ideas has wrought a change in this uncompromising attitude. In the first place the rapid progress made in recent years in the control of "tropical" diseases bids fair to reduce very considerably, if not to abolish, the most obvious barrier to adjustment. Secondly, there is abroad a very strong spirit of nationalism, which raises questions whether the indigenous man and the indigenous culture may not, after all, be more in harmony with the local conditions. Thirdly, the number is daily increasing of those who genuinely think that practical international co-operation, such as is expressed through the support of United Nations activities, recovery programs, Point Four proposals and so forth, is the only road to world security. The time is ripe for a dispassionate re-examination of the triple interaction of northern man with temperate culture, tropical environments, and tropical peoples with their cultures. Much of this lies in the realm of psychology; much of it is germane to the applied sociologic fields of study, but much of it requires at least a thorough appreciation of the basic physiologic reactions of man to the conditions prevailing in tropical regions.

In 1925 Cilento[2] wrote of tropical problems ". . . it is difficult to apply . . . the specialized observations made by laboratory workers in physiology or biochemistry . . . since from the considerable series of investigations there have arisen masses of tabulated minutiae, which, to all intents and purposes, are mutually contradictory." Twenty-five years later a clinician picking up the latest book to be published

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‡A most interesting speculative account is presented by Heard.[1]

on the subject[3] may well wonder whether, in spite of the tremendous advances there recorded, sufficient system has been introduced into this field of study. As a matter of fact, such a judgment would be harsh, for there has arisen quite a systematic approach to the problem of man versus climate, and much of the detailed advance has depended upon, as well as contributed to, the emergence of this systematization. The trouble is that most technical papers are written by technical specialists, for technical specialists and about special technical points. Each chapter in the book referred to is an excellent account of a special area, but nowhere in it is the field as a whole adequately presented, or the systematic approach simply illustrated.

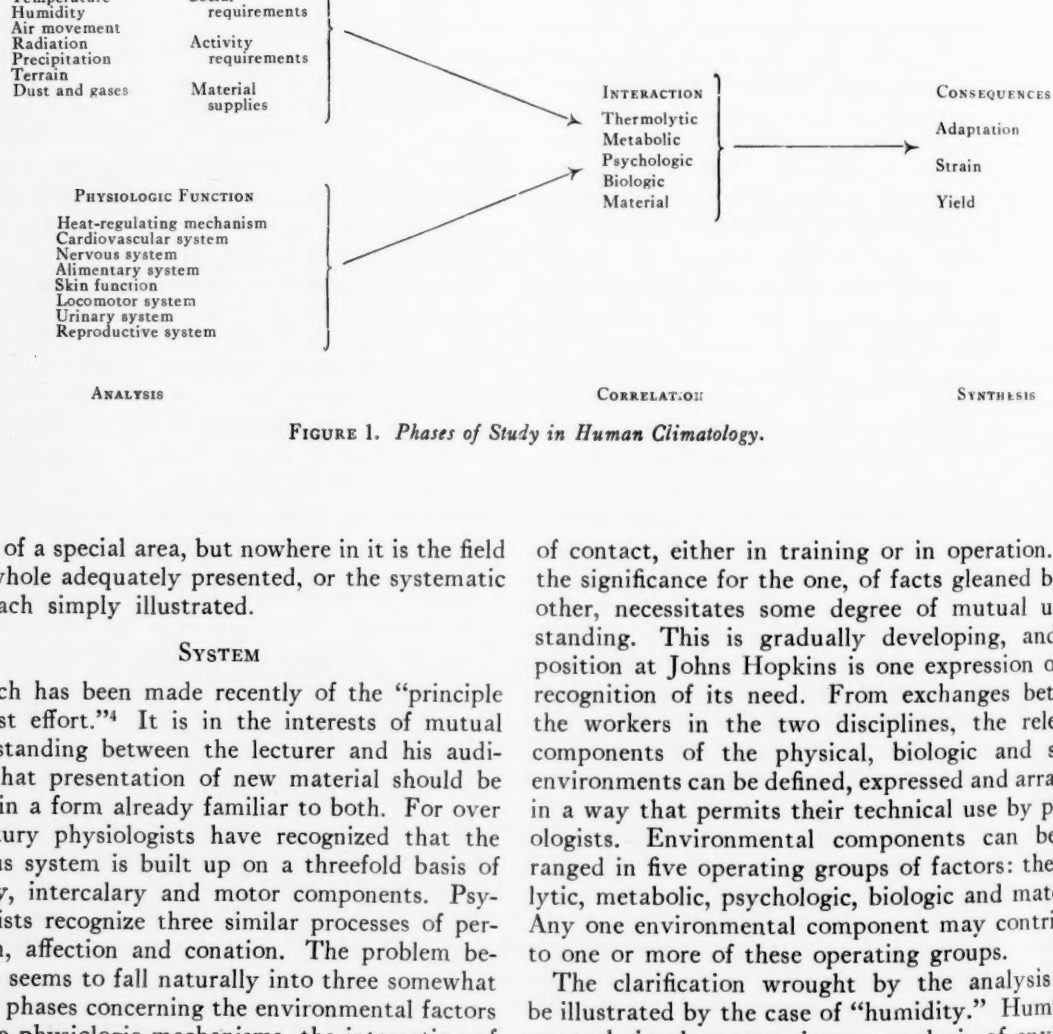

FIGURE 1. *Phases of Study in Human Climatology.*

System

Much has been made recently of the "principle of least effort."[4] It is in the interests of mutual understanding between the lecturer and his audience that presentation of new material should be made in a form already familiar to both. For over a century physiologists have recognized that the nervous system is built up on a threefold basis of sensory, intercalary and motor components. Psychologists recognize three similar processes of perception, affection and conation. The problem before us seems to fall naturally into three somewhat similar phases concerning the environmental factors and the physiologic mechanisms, the interaction of the environmental factors with the physiologic mechanisms and the consequences of such interactions for the system as a whole (Fig. 1). The corresponding mental orientations required of the investigator are analysis, correlation and synthesis. To detail the processes would take more time and call for more patience than we could expect of ourselves on this occasion; to list the items for consideration would be tedious and pointless. In the words of my favorite philosopher, Kai Lung, invented by Ernest Bramah, "There is a time to speak in hyperbole and a time to frame words to the limit of a narrow edge."

The analytic procedure, we have seen, must be applied in two fields: that of the environment and that of the physiologic mechanisms. Studies in these two fields are normally conducted by two different groups of workers, with but few points of contact, either in training or in operation. Yet the significance for the one, of facts gleaned by the other, necessitates some degree of mutual understanding. This is gradually developing, and my position at Johns Hopkins is one expression of the recognition of its need. From exchanges between the workers in the two disciplines, the relevant components of the physical, biologic and social environments can be defined, expressed and arranged in a way that permits their technical use by physiologists. Environmental components can be arranged in five operating groups of factors: thermolytic, metabolic, psychologic, biologic and material. Any one environmental component may contribute to one or more of these operating groups.

The clarification wrought by the analysis can be illustrated by the case of "humidity." Humidity must obviously appear in any analysis of environmental items affecting man in hot regions. For physiologic purposes it had to be realized that what we usually require to know is the vapor pressure, whereas the datum usually quoted in meteorologic reports is the relative humidity. Explanation, understanding and revision of practice is thus neces-

sary to permit utilization of meteorologic data on humidity. Some progress has been made, but it will be a long time before massed data are available in suitable form. In the course of the discussions, the physiologist has learned something of the meteorologic determinants of such items as atmospheric vapor pressure, and has thus acquired some geographic orientation for the application of his ideas.

Crystallization of ideas regarding the physiologic complex upon which environmental factors operate was likewise necessary. This is the physiologist's own field, but it has required the technically uninformed queries of the climatologist to bring him to the point of framing adequate, but simple, presentations. Anyone who has taught systematic physiology knows how difficult it is to find a starting point that does not involve considerations of systems yet to be discussed and thus, for the moment, unknown to the listener. One does not need a ground plan to find the way about one's own factory, and one hopes that the apprentice will stay long enough to become equally familiar with the layout. But for the visiting consultant, who is trying to help and whose time is limited, such an aid to location is very desirable. The climatic physiologist, therefore, must have some such plan of the complicated physiologic mechanisms for the guidance of his nonphysiologic colleagues. He should not be surprised if, in the course of preparing it, he finds that he himself was quite "woolly" on some of the interrelations.

By such processes of analysis and classification of environmental items on the one hand, and of physiologic mechanisms on the other, the basis has developed for exact consideration of the interaction between them. It has become possible, for example, not only to discuss the effect of variations in atmospheric vapor pressure (or, alternatively, absolute humidity), upon such first-order processes as heat exchange between the body and the atmosphere, skin wetness, wetness of the upper respiratory tract and efficiency of mechanical effort, but also to follow through, in fairly direct fashion, the consequential effects upon such bodily processes as skin temperature, sweating, disturbances of epithelial function, sensations of comfort, psychologic attitudes and metabolic activity. It has become possible to do this with some precision and with conscious appreciation of the relation that each item bears to other processes in the environment or in the body. When some modification in the environment or in its impact upon the body is proposed — by air-conditioning, by clothing or simply by running away — the consequences of that modification can be traced through with some certainty that important effects will not be overlooked.

More complicated interrelations exist than those attendant upon the operation of atmospheric humidity, or at least than those I have mentioned as attendant upon it, but my purpose is to illustrate, not to confuse. Actually, of course, the more complex the interrelations, the more necessary is a plan. But by this time, many of you will be posing a variant of a question that bothers many an intellectual physician — having resolved a problem into a series of special questions, how do we put the information together again in answer to the original problem?

Most of us received our basic instruction in scientific method from men who were primarily physicists, chemists and mathematicians. For the relatively fixed, precisely measurable materials or phenomena with which they were accustomed to deal, the process of resynthesis presented no special problem; an adequate analysis of the problem was the essential. But if a biologist finds his material and processes remaining fixed, he generally suspects that they are no longer biologic. There is, for him, no simple rule for adding particulate results together. Yet there is no point in an elaborate analysis whose results cannot be integrated, and practical affairs will not stand still because the analytic scientist has reached a state of perfect disintegration. Some method must be employed for using the results of analysis in the interests of the whole. What is it?

The answer can be found in a simple illustration from our daily behavior. At a busy intersection, it would be possible for a driver to estimate the speed and direction of each vehicle, plot them and determine by calculation a course free of the risk of collision. But practical considerations (including the risk of collision with the forces of the law) preclude such erudite behavior, and the driver actually proceeds by a species of "clinical judgment." To a physiologist, there is nothing fantastic in the suggestion that the nervous system can behave like a modern high-speed calculator, performing essentially the same determinations as the hand-driven slide rule, but at a greatly increased rate. The climatic physiologist, like the driver, familiar by long association with the nature and properties of the interacting environment and human body, can arrive at certain practical principles, and perhaps even specific solutions, by a process of "clinical judgment." There is this difference, however, that the integrative processes submitted to a calculator and those behind driving across an intersection are both susceptible of precise mathematical formulation, whereas those with which we are here concerned are not. The chief effect of this is that the pattern of integration must be determined by experience of the verity of the conclusions, and must be continually reinforced by such checking. Provided that these integrative thought processes are sufficiently practiced and reinforced by experience, increased familiarity with the raw data at various stages of analysis, and with the analytic processes themselves, can serve only to improve the quality of

the end product. No one of the three stages of study—analysis, co-ordination or synthesis — is supreme; all are equally essential, and all are interdependent in the development of a better understanding and better handling of practical problems in human adjustment to hot environments.

Results

Dr. John Clarence Cutter, whose memory we honor here this evening, was a man who had devoted a considerable portion of his life to a study of the detailed physiologic processes of the human body; yet he could, when the necessity arose, see the problem as a whole and, seeing it as a whole, select the correct bit of particular knowledge to fit the particular aspect that needed most urgent action. You may well be asking yourselves, by now, whether all this attention to the organization of inquiry might not obscure, rather than clarify, the practical problems of the moment. After listening patiently to the recital of one who has been down into the mine, and his tales of the riches to be found therein, you may well be excused for requesting a look at the actual products and a chance of testing their usefulness. Can we, now or in the near future, gain, from the systematic study that I have described, knowledge upon which to base, with some assurance, action appropriate to various particular aspects of tropical adaptation? In particular, can Dr. Cutter's purpose in providing for public lectures in preventive medicine be served?

In laying some of the conclusions before you, so that you can judge for yourselves the acceptability of the first-fruits of this labor, let me begin with the question of the magnitude of the tropical problem. Are tropical climates, in general, so inimical to temperate standards of activity that civilization, as we understand it, is virtually impossible?

The more one goes back and forth over the evidence, the more one is brought to the belief that the direct effects of tropical climates upon man do not constitute a very serious barrier to the development of productivity comparable to that of typical temperate civilizations. Certain adjustments in the mode of living and working must be made, however. The objects of temperate civilization can be largely realized, but its trappings require considerable modification. There are, moreover, many difficulties, other than the direct effect of tropical climates upon man, that may interfere with the realization of those objects. Tropical disease has been mentioned as coming more and more under control, but there remain the effects of climate upon plants and domestic animals (which are much more reactive than man), the aridity of soil in some parts and its leaching in others, shortage of labor in some regions and the social inertia of dense overpopulation in others, unfavorable relation to world markets and several other influential circumstances. Characterization and solution of these difficulties are beyond our scope here, and we must confine ourselves to discussing what can be done to help the physiologic adjustment of man where other circumstances make it desirable that he should live.

Consideration of physical aids to adjustment at once indicates the necessity for distinguishing between hot dry and warm humid environments, even though the total heat load may be the same in the two cases. In the former, exclusion of environmental heat from access to the body must be the principal objective, relatively little attention being required to the facilitation of evaporation from the body. In the latter, it is evaporation from the body that must be promoted, sometimes even at the expense of protection against solar radiation. Although hot dry and warm humid conditions may alternate and call for some ingenuity in providing flexibility of protective measures, high temperatures and high vapor pressures seldom occur together. (Certain parts of the Persian Gulf coast constitute an exception to this.) These principles are fundamental in the design of both clothing[5] and housing[6] and have to be taken into account even in air conditioning. Their neglect has been the cause of much unnecessary discomfort and loss of efficiency in the past. (Confused by extraneous cultural factors though they are, the habits of peoples long indigenous to typical hot dry and hot humid regions could have led us long ago to a recognition of the importance of these principles.) The exact way in which these principles should be applied will vary with all sorts of particular circumstances — cultural, religious and material. Important concessions may sometimes have to be made to special circumstances, but this should be done only with a clear implication of the thermal consequences.

On the subject of air conditioning my own reactions are somewhat conservative. When we are dealing with a frank ex-plant of the temperate culture and the personnel are essentially "sojourners,"[7] full-scale air conditioning of offices and houses is probably desirable, if the cost can be withstood. But for permanent residence, some compromise has to be effected with the natural climate, and in such cases I should not recommend more than counteracting the extra heat load in the kitchen and in hot industry, removing real discomfort in sleeping quarters and providing a refreshing change in public facilities for recreation. To cool offices and leave homes untreated is not very good physiology.

Advice on physiologic adjustments clearly involves "clinical judgment," and in this regard, activity obviously presents the most difficult situation. Temperate civilization is characterized by activity, which has consequently acquired a considerable significance in the structure of individual as well as social morale. The Arab, or the Fijian, feels no sense of guilt when he spends days in idle, social converse; he is not guilty, and he suffers no

loss of morale. But if the Westerner habitually does likewise, not only does he feel guilty but he is guilty. If he were not inferior before, he will certainly become so by the very fact of defaulting on acknowledged social responsibilities. Consideration of the thermal balance alone may suggest the advisability of being as inactive as possible in hot climates, but Western civilization demands a relatively high degree of activity. What is the answer?

Observation of different animals in experimental hot rooms indicates that it is not always the inactive individual or breed that has the higher heat tolerance. It frequently happens that the animal that keeps standing and maintains a certain alertness gets on better. Human experience indicates that the person who maintains a certain degree of physical activity in hot weather comes off best. Cause and effect, physiology and psychology, are mixed up in this to a certain extent, but the practical suggestion agrees with social requirement — that activity is desirable, up to the point that an adverse response can be demonstrated. I once shocked an Indian Army brigadier by advocating activity as a preventive of summer inefficiency, but I was agreeably surprised, a few weeks ago, to have the Government Medical Officer at Bahrein, Arabia, offer the same advice — without prompting from me. (Bahrein is one of the few places where high vapor pressures accompany high temperatures.)

Although there is a great deal to be said for the maintenance of activity, this must not be extended uncritically to mere maintenance of a high metabolic rate. The one series of observations on the comparative reactions of different races of heat in which I have faith is that by the staff of the Harvard Fatigue Laboratory, on Negro and white sharecroppers.[8,9] It appears from this study that, at medium levels of activity, the Negroes worked more efficiently than the whites — that is, they expended less total energy and therefore produced less heat for the same performance of external work. It is a matter of common observation that many Negroes, when there is no call to perform external work, spend as little energy as possible. The same sort of thing could be observed in white troops as they became accustomed to the conditions of New Guinea. When engaged in necessary activity — and this sometimes reached very high levels — they worked well, efficiently and with surprisingly little physiologic disturbance. When activity was not required, activity did not occur. When one was required to move from point A to point B, he did so with the minimum of effort; when he arrived, that effort ceased. The important decision, for administrator and individual alike, is where to make the distinction between saving of unnecessary heat production and maintenance of that activity which is necessary, on both physiologic and psychologic grounds, for general welfare.

The question of the duration and arrangement of work periods is one on which more study is required. My present opinion is that there is no great need to change the duration of sedentary or moderately active work from that customary in temperate climates, but that hard physical work may call for more frequent rest pauses and perhaps, if the conditions are unusually severe, some reduction in the total duration. I personally do not favor the siesta, on the grounds that a normal lunch hour is long enough for a mid-work break, that a practicable siesta is not long enough for sleep and comes at a time when sleep is difficult, that it means starting the day twice and that it subtracts from the cooler hours in which relaxation and sleep are more possible and beneficial. If the work period is started early in the day, the hot hours (1:30 to 3:30 p.m.) come toward the end, and can be tolerated better because of the proximity of that end. It is the sedentary worker who feels the depressing effect of the hot hours most, and this can often be countered by arranging for some mild physical activity to come at this time. I shall return a little later to psychologic matters.

The next most important physiologic consideration centers on the maintenance of the water balance. Experienced subjects in experiments usually allow a certain degree of dehydration to develop in the course of acute exposures. Forced maintenance of body weight by water drinking in these subjects often results only in pyloric closure and subsequent vomiting. Newcomers to the tropics appear to drink water more frequently than residents do. The figure of 1500 cc., given in textbooks as the normal daily urine volume for temperate climates, is not maintained in hot weather (I suspect that more than one patient's lungs have been flooded in an enthusiastic attempt to restore this fictitious norm by intravenous therapy); 800 to 1000 cc. is the usual volume. In some cases it falls lower than this, but this is to invite urinary calculus, if not actual loss of renal efficiency. Although no exact figures are available, so many medical men report an unusually high incidence of urinary calculus in the tropics that it may be accepted as probably true. It seems, therefore, that a certain proportion of tropical residents would be well advised to take more water, not only "with it" but at all times.

The necessity for replacing salt as well as water is now very well known — perhaps too well known! I sometimes wonder if the consumption of large numbers of salt tablets has not become something of a fetish. Some 12 gm. or more of excess salt is thrown away daily in the urine of the temperate dweller on a normal Western diet. The sweat of acclimatized whites often contains less than 1 gm. per liter. A man has to be working fairly hard, and under quite hot (and dry) conditions, to lose an *average* of half a liter of sweat per hour through the whole twenty-four hours. (I doubt very much the

necessity of putting salt tablets next to the drinking fountains in Washington offices.) My own recommendations are as follows:

Conditions	Acclimatization	Work	Daily Extra Requirement
			gm.
Warm humid	Acclimatized	Moderate to heavy	—
Warm humid	Unacclimatized	Moderate to heavy	7
Hot dry	Acclimatized	Moderate to heavy	
Hot dry	Unacclimatized	Moderate	
Hot dry	Unacclimatized	Heavy	14
Very hot	Acclimatized	Moderate to heavy	
Very hot	Unacclimatized	Moderate to heavy	21

Skin disturbances were very common in the South West Pacific. Macpherson,[10] my principal assistant in wartime studies, found that 57 per cent of men he examined had developed one or more skin lesions; 18 per cent of the lesions were severe. Of 100,000 available man days in this force, at least 800 were rendered completely and at least 9000 partially noneffective. The pathology of the most common type was determined independently by American and Australian investigators.[11-13] The essential process is one first of swelling of superficial epithelium and then of proliferation, with plugging of the sweat glands. Irritation and cessation of sweating result. "Prickly heat" gives place either to frank dermatitis or to anidrosis. Continual wetness of the skin, friction and removal of sebaceous fat by excessive use of soap, combine to produce this condition. Aeration of skin, reduction of friction and less enthusiastic use of soap are indicated — antiseptic applications are not.

When we turn to psychologic responses to hot conditions, we enter a realm where the threads between clinical judgment and classically scientific proof become tenuous indeed; yet judgments must be made. In one respect at least, a plausible physiologic explanation can be advanced for observed psychologic reactions. Under severely hot conditions, a degree of peripheral vascular failure and a degree of cerebral dysfunction occur together, as cause and effect, in the syndrome of heat exhaustion.[14] With lesser degrees of heating, the symptoms may be nothing more than a general feeling of weakness and lassitude. It is quite possible that the general disinclination for work and the spirit of mañana that commonly occurs in tropical regions has its root in long-continued or oft-repeated cerebral ischemia of low degree. It should also be remembered that the active cells of the heat-regulating "centers" are in close association with other hypothalamic cells, often loosely referred to as the "sleep center." It is quite possible that activity in the former irradiates to the latter and assists in producing feelings of lassitude, inattentiveness and drowsiness. Whatever the mechanism of their production, these feelings are very real and have considerable significance for the continuance and efficiency of sedentary work. Physical activity, or incidents to capture the interest, will usually remove the inhibitory processes, and are to be sought in planning of daily activity, especially during the hottest hours. Heavy meals notoriously favor drowsiness, and should be avoided if the continuance of initiative and mental activity is required in the subsequent hour or so. Alcohol, through its dilating effect upon blood vessels, and possibly through the production of a relative dehydration, is even more effective in promoting disinclination for work in the tropics than it is elsewhere — as well as providing an easy escape from conditions or action that may appear unattractive.

Fortunate indeed are the few, in any walk of life, who never encounter conditions from which they would like to escape! It is debatable whether the sum total of such conditions is greater in the tropics than elsewhere — at least for people who voluntarily elect to work and live there. On the other hand, it is probable that the margin of tolerance is somewhat reduced, if only for the reasons already suggested. But success, in the long run, depends upon facing problems, not in running away. Anything that fosters escape is not only antisocial but also against a person's own interests. As Macpherson[10] puts it, when climate is aggressive, it must be met with aggression. The modes of escape are numerous and subtle. To quote Macpherson[10]:

> In the course of taking medical histories, it became evident that a group of symptoms occurred together so frequently that it was considered that they constituted quite a definite syndrome. They were: — sleeplessness, headache, vague abdominal pain, loss of appetite, pains in the back, loss of weight, dizziness on standing up, i.e., the so-called "blackouts." If a man volunteered a complaint of one or more of these symptoms, questioning soon revealed a claim to suffer from the remainder as well . . . It may be said that the patient does probably observe all these phenomena but it is the heightened sensitivity, compelling him to elevate them to the dignity of symptoms, that marks him as neurotic or mentally inadequate to to the circumstances in which he finds himself.

Alcohol has been mentioned, but equally effective are continued refusal to identify oneself with the community and region, postponement of decisions upon personal regimen and acceptance of traditions of minimum activity. For one trained in Western standards of activity, continuation along such lines will lead either to abandonment of the intangible cultural possessions that Western civilizations have built up by centuries of effort or to the neurasthenia that comes from vacillation. It is true, as I pointed out at the beginning, that adjustments and compromises are necessary. The important standards and ideals of the parent civilization must be maintained, but the details of daily behavior must be modified to conform to the physical and other environmental conditions of the tropical region. The change, moreover, must be by decision and not by default.

It may be considered unwise of a physiologist to have ventured opinions on psychologic matters, even with the justification I have given. But I

am now about to seek your further indulgence for some final comments on community problems, and for this my sole excuse is that I feel quite strongly about them. Although it will be necessary, for at least some time to come, for a certain number of people to be mere visitors or "sojourners" in the tropics,[7] the influential mass of any community must be permanent residents, if stability is to be achieved. Indigenous members, in accepting the ideas of temperate cultures, must seek a workable integration of those ideas with local cultures and an adaptation of them to local conditions. Immigrant members must not only adapt their customs to local conditions but also stop regarding themselves as anything but members of the new community. The new location must be "home," with all that implies — the place where they will live, work, and die, the place where their children will grow up and the place to which they belong and for which, as well as in which, they strive. To this end they must develop all possible services and amenities necessary to the immanent culture. This is true not only for such material requirements as housing and sanitation but also for long-range projects such as education. Not only kindergartens but grade schools, not only grade schools but high schools, and not only high schools but colleges and universities must be provided whenever possible. The two tragedies to which colonial officers are apt to be exposed is the removal of children to the home country and their own compulsory removal at retirement from the scene of their life work. It is impossible to develop coherence or singleness of purpose in a community thus split in loyalties, prejudices and aspirations.

This centralization of life upon the local community requires a definite attitude toward vacation periods. The word "leave" carries with it the implication of a temporary release from unattractive duty and, in colonial practice at least, a respite at "home" — that is, in the parent country. The normal American term "vacation" could very well be used in its place by all English-speaking communities, since this is simply a period in which customary daily activities are vacated in the interests of recreation; it is a period of essentially centrifugal orientation, a browsing in new pastures, not one of centripetal flight, a running home to mother. In view of the relative isolation, and the somewhat more pressing environment, there is a case for making the vacation period somewhat longer than is customary in temperate communities, and for material assistance in transportation, but these should be regarded as simple adjustments, not as rewards for arduous service.

On the delicate question of "underprivileged groups," what I have to say could be predicted from what has gone before. From the physiologic point of view, it is desirable that heavy physical work and unattractive or monotonous work be minimized in hot climates. It is only human that these tasks should be relegated to the members of any underprivileged group that happens to be present. It is only natural, also, that the underprivileged will be disinclined to exercise much personal effort to combat the lethargy invoked by the climate. For these reasons, the ratio of unskilled to skilled labor is likely to be greater in the tropics. This tendency by its very naturalness introduces a real danger, and one that has militated very severely in the past against successful development of tropical areas by Europeans. Unskilled labor must not be used to the point of exempting the more skilled from all manual effort; especially must it not be used to the point of making such exemption a matter of "face." To make exemption from manual effort a badge of social superiority in any climate is contrary to sound mental hygiene and does much to promote neurasthenic manifestations in those who wear it.

If the material from books on the tropics by various writers is carefully examined, and more particularly if the authors are closely questioned, it transpires that the major difference between optimists like Hanson[15] and pessimists like Vogt[16] lies in their judgment, not of physical facts and resources, but of human behavior and institutions. The crucial question usually is, not what *ought* or even "what *can* be done," but "what *will* be done." In the final analysis, it is the art of "man management" that determines the rate of progress, for history has ever shown that the application of new knowledge lags behind its acquisition. The physiologic evidence that we have reviewed, though sketchily, clearly indicates, not only that man management is more important under hot conditions but also that it is likely to be dulled by the physiologic stresses of the environment it is called upon to counter. The climatic physiologist has a responsibility not merely to report his conclusions on this subject but also to bring a realization of its reality and importance home to those responsible for directing policy and administration in tropical areas. It may be true that any one scientist may not see sufficient improvement within his own active lifetime to justify an overweening pride in his achievements, but the effort must be made, and made continuously. It is true that his conclusions will continually be challenged by the establishment of new facts and clearer interpretation of the old, but he must effect the reconciliation in the spirit of Leeuwenhoek, with whose words[17] I may fittingly conclude:

> I well know, most noble Sirs, that the propositions I come to make, and which I've sent you from time to time, do not all agree with one another, but contradictions are to be found among them: so I will only say once more that 'tis my habit to hold fast to my notions only till I'm better informed, or till my observations make me go over to others: and I'll never be ashamed thus to chop and change.

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THE ROLE OF THE NONTEACHING HOSPITAL IN MEDICAL EDUCATION*

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THE title of this paper should have been "The Role of the *So-Called* Nonteaching Hospital in Medical Education." In fact education is an essential function of every hospital that intends to do a complete job. The use of the terms teaching and nonteaching hospitals is widespread, but they refer to whether or not a hospital is engaged in the instruction of medical students. Postgraduate education is nearly as important as undergraduate instruction, and opportunities for residency training are needed beyond the facilities offered by university teaching hospitals. Whether or not one agrees that the trend toward specialty-board certification has gone too far there is little doubt that this movement has improved standards of medical care throughout the country and is here to stay, though perhaps with modifications.

Not only is there a need for opportunities for residency training outside university teaching hospitals but also a teaching program is essential for the practicing physician. The revolutionary developments in diagnosis and treatment of patients that have taken place in the past few years leave no doubt that the life history of every doctor must be one of continuous self-education if he is to fulfill an adequate service to his patients. Although some doctors can attain this by reading, attendance at meetings or taking short refresher courses each year, the best way to achieve this continual educational process is a teaching program in the community hospital. Teaching is possible in any hospital, but it requires the co-operation of the staff, the leadership of someone who will take responsibility for supervising it and support of the board of trustees, who should be aware of the necessity for education in the hospital to the extent of making provision for funds, for it does cost money.

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The role of the so-called nonteaching hospital in medical education may be considered under four headings: continuing education of the attending staff; education of interns and residents; clinical investigation; and co-operation with a medical center and with other hospitals. Obviously, these four aspects of the problem are all interrelated.

CONTINUING EDUCATION OF THE ATTENDING STAFF

To develop a teaching program for the staff certain criteria need to be fulfilled. An educational director who will take responsibility for organizing clinical conferences, lectures and pathological and other teaching exercises should be appointed. There is always ample clinical material of educational value in any hospital that can be organized and made available for the educational benefit of the staff. To do this requires that someone make the effort to do it effectively. Such a person needs to be compensated for his time in order that he may put this responsibility ahead of other duties. Furthermore, the staff needs to develop the attitude that private patients are not personal property but may be discussed at clinical conferences and teaching rounds for the educational benefit of all. Inevitably, this leads to marked advantages to the patient himself, not only in the immediate problem but also by improving general standards of medical care. Financing the greater costs resulting from an educational program should be recognized as a necessary part of the hospital budget, not as a luxury but as an important factor in providing the best of medical care to the public. Actually, the increased costs may be largely offset by better care, resulting in shorter hospitalization, avoidance of ill advised therapy, unnecessary surgery and so forth.

EDUCATION OF INTERNS AND RESIDENTS

The hospital that is so well organized as to be able to attract house officers is indeed fortunate.

There are twice as many approved internships in the country as there are applicants for the positions. Why is a house staff a desirable adjunct to a hospital? Certainly, it must not be for the chief purpose of shifting some of the load of routine work, emergency night work, keeping of records and so forth onto a young doctor in training. If this is the object house officers will not and should not be attracted to a hospital. This work will be willingly done, however, provided there is a spirit of teaching in the attending staff and an educational program from which the house staff can benefit. In return these young doctors will give a marked stimulus to the older man by keeping him abreast of the latest advances in medicine and will be the spur of the educational program.

Development of educational programs sufficiently good to attract a house staff will have a marked influence in attracting good general physicians to communities removed from a medical center. One of the main difficulties in persuading highly trained physicians to practice away from medical centers is the frequent absence of opportunities for continuing their education, and a lack of intellectual stimulation. If the community hospital in outlying districts is well organized from the educational point of view this obstacle to the attraction of good doctors is overcome, and there will be a greater incentive for men to become general physicians rather than specialists, with which the country is oversupplied.

In addition to being of marked value as an educational stimulus to the hospital the presence of a house staff results in better care for the patients. An alert house officer is extremely thorough in his examination of patients. He turns to the library for information in obscure problems and often makes valuable suggestions to the attending physicians. Although these suggestions may relate to the possibility of some rare disease recently learned in medical school and only remotely possible in the case at hand, the mere consideration of all possibilities leads to greater accuracy in diagnosis. The busy general practitioner who rarely sees the unusual condition tends to let these possibilities slip out of his mind. So the house officer keeps the older physician more alert, making his diagnostic acumen more acute. With the revolutionary changes rapidly taking place the physician's therapeutic skill is often enhanced as the result of suggestions from the house staff.

Do patients, especially private patients, appreciate the attentions of interns and residents? From my own experience with a residency training program in a medium-sized suburban hospital there is no question that the vast majority do. Rarely are there complaints of too many doctors examining the patient. More often, there are expressions of gratitude for increased attention, and of appreciation for the security of knowing a doctor is always at hand. On the medical service regular teaching rounds are conducted by a teacher assigned for a month at a time, at which private patients of other doctors are seen and examined. Although tact is obviously required (and where is it not required, no matter what the type of hospital?) the objections raised by patients to these teaching rounds are so few as to be insignificant, and the doctor-patient relationship has not suffered.

The autopsy percentage of a hospital is an accurate index not only of the quality of work being done and the degree of interest in scientific medicine but also of the appreciation of families for the attention, care and skill that have been exercised in the treatment of the patient who has died. At the Faulkner Hospital before the development of a highly competent house staff, on the medical service the autopsy percentage for six months was 50 per cent for 32 deaths. During the six months following the arrival of a very able group of house officers there happened to be the same number of deaths, but the autopsy percentage rose to 82 per cent. At the same time medical admissions rose an average of 18 per cent each month, which seems to reflect an appreciation for the improved over-all care patients were receiving from a good house staff.

Another very important contribution that the house staff makes to a hospital is an improvement in records. Busy practitioners are less likely to write detailed histories or frequent progress notes, and may not exercise the same diligence in recording the exact diagnosis and secondary diagnoses on the discharge note of the patient. Yet completeness and accuracy of records are often of great value in the future care of the patient, as well as to staff members who may at some later date wish to make some statistical study and to the surgeon who may wish to review his results. House officers should make the most complete and accurate records possible in each case, for this is essential for their best training.

Defraying the cost to the hospital of an educational program and of a house staff is a problem that often has not been met squarely. Usually, the cost is absorbed into the budget without specific provisions to meet it. There should be a greater awareness on the part of boards of trustees and also of the public that these elements of a hospital are a direct advantage to the patient. Because of this it would not be unreasonable to make a fixed charge for house-officer services, just as there may be a fixed laboratory fee. Blue Cross might justifiably recognize it as one of the ancillary services to be covered by the contract. It has also been suggested that staff members might be assessed a small sum for each patient admitted inasmuch as the house staff saves so much of their time in care of records and acting as assistants.

There are certain necessary requirements that a hospital must fulfill to give adequate postgraduate

training to interns or residents. The first is the matter of sharing in the care of private patients. It has long been assumed that only ward or service cases should be seen and examined by the house staff. My experience has been that actually there is no problem in allowing house officers to examine private patients, to see them daily and to take as much responsibility as their training and experience will allow. It is true that diffusion of responsibility may create problems at times, but these can be minimized by adequate supervision. In at least one university hospital all the patients are private, and yet this hospital makes use of the patients not only for teaching of house officers but also for students as clinical clerks in the same way as in a ward service of charity patients. It is well that this distinction is being obliterated, for with the great increase in voluntary health insurance more and more patients are private. Certainly, medical education and clinical research must continue, so that ways must be found whereby private patients may be used for these purposes. On surgical services the problem is more complex, for it is more difficult to give a surgical resident staff increasing surgical responsibility in the operating room than it is in training internists and general physicians. On the medical service of the Faulkner Hospital it has been possible to provide a comprehensive educational program. With a 40-bed service in which 90 per cent of the patients are private, and an average daily census of 30, with a rapid turnover, there is enough work for a resident, 2 assistant residents and an intern. The resident supervises the house officers under him, is responsible for the entire service and has a portion of his time free for investigative work. Daily organized teaching rounds of an hour and a half are held, and there are weekly x-ray, pathological and electrocardiographic conferences for the house staff, as well as a weekly grand rounds run by the residents and attended by about 30 members of the visiting staff.

In addition to the value that an organized educational program can give to the hospital and thus to the patient, the house staff receives certain benefits from training in a so-called nonteaching suburban or community hospital that cannot be obtained at a large university teaching hospital. In the latter hospital the patients, as a rule, are highly screened. They often come from a distance and are likely to have diseases that are rare or uncommon because the staff is more highly specialized than that at a community hospital. Thus, the students and house officers tend to receive a false impression of the incidence of disease. Furthermore, the university teaching hospital is not, as a rule, staffed by physicians who take care of the patients as the family physician. In a community hospital with private patients the house officer is in close contact with the physician who has been caring for the patient from the onset of first symptoms of the illness, and will obtain follow-up information from the physician, whom he sees every day, after the patient has been discharged. He thus has closer contact with the beginnings of illness and with the problems of convalescence. Morover, he is more likely to become aware of the personal problems in the management of patients and their families. He will have more direct responsibility than in a university center, where there are numerous echelons of responsibility from the student up to the professor. He can learn much from the family physician, with whom he is in daily contact and will also learn that many laboratory procedures, done routinely in a teaching hospital, often for research purposes or for teaching about disease per se, are unnecessary in the actual management of the patient. Indiscriminate use of the laboratory and x-ray department is one of the weaknesses of American medical education, tending to reduce reliance on history taking, clinical judgment and knowledge of the patient as a person.

The use of the term "psychosomatic medicine," as if it were something new, has become widespread in this country. In terms of research psychosomatic medicine may justifiably be considered an independent discipline, but regarding treatment of patients it is hardly more than *good* medicine with equal consideration of all factors involving the patient — physical, emotional and environmental — and with the special therapeutic skill of the psychiatrist called upon when indicated. The somewhat confused emphasis on psychosomatic medicine in this country may be partly a result of the isolation of the hospital patient from the physician who really knows him from taking care of numerous minor ailments and who knows his failings and his vagaries through knowledge of his family setting and as a member of a community. However, the psychosomatic point of view in medicine or, in other words, consideration of the patient as a whole is one of the essential attributes of the family physician. When he is a member of the staff, engaged in teaching house officers, his influence can be great in developing this important quality in the practicing physician.

Clinical Investigation

The care of the patient, teaching and research are three functions of a hospital. Research, an attitude of mind looking for opportunities to add increments of knowledge, is not a prerogative of the research institute or the university alone. Fundamental laboratory research as a rule is not feasible in the nonteaching hospital, and yet clinical investigation of patients by means of the statistical method of case studies, follow-up study of patients or simple laboratory investigations is possible in any hospital. Clinical investigation improves teaching, stimulates careful and critical work and thus adds to better care of the patient. The busy prac-

titioner usually has little time for this work, but an organized house staff with an experienced resident may carry on such investigations with the supervision and stimulation of members of the attending staff. This should be encouraged, since it tends to improve the caliber of the work and of the thinking of the hospital staff. Needless to say this type of clinical investigation requires complete and accurate records, which are best achieved when a house staff is actively engaged in the examination and care of all the patients.

Co-operation with a Medical Center and Other Hospitals

An aspect of medical education that has been developing rapidly since the war is the integration of regional nonteaching hospitals with a medical center and medical school. In New England this is best exemplified by the New England Medical Center plan, inaugurated in 1936, whereby community hospitals throughout New England are organized to work with the Center. Residents are sent to outlying hospitals to supervise and organize a teaching program. Physicians come to the Center for postgraduate courses, and teachers go to the peripheral hospitals for lectures, conferences and other teaching exercises. In this scheme the university teaching center is closely integrated with community hospitals and practicing physicians. Regional hospital integration with a medical center has also been developed in other parts of the country — at the University of Rochester, the University of Michigan and New York University-Bellevue Medical Center. Lessening the isolation of the medical teaching center from the community hospital and the practicing physician is undoubtedly an important development in medical education. The teaching hospital is inevitably staffed with specialists, and the residencies are taken up by physicians who usually intend to become specialists. Thus, the medical student sees many specialists but few general physicians. It is not surprising that he may conclude that a career as family physician is not worth while. Rotation of residents through the community hospital will inevitably result in a broader point of view.

What I have tried to express may be summarized as a consideration of how the best qualities of the university teaching hospital, as they concern the care of patients, may be diffused into nonteaching hospitals not connected with a medical school. These qualities of an inquiring attitude into the nature of disease, a desire to impart information to others and complete co-operation on the part of the staff for the best interests of patients are usually better attained in the university center than in the nonteaching hospital. At the same time the nonteaching regional hospital, by virtue of its functioning at a different level close to the patient and the family physician, has many attributes that the university teaching center lacks. The attributes of both are needed in medical education, and the more they can be blended, the better will be the practicing physician of the future.

Summary

Medical education is a lifelong process for every physician. This can be achieved most effectively through carefully organized teaching programs in all hospitals.

In the postgraduate education of interns and residents the so-called nonteaching or community hospital can play an important role. The regional hospital, staffed largely by general physicians caring for patients both in the hospital and at home, may provide a point of view regarding the patient as a whole that is less well developed in the university teaching hospital setting but is essential to the education of the practicing physician.

Co-operation between medical teaching centers and outlying hospitals is being developed, with mutual advantage to both center and periphery.

SOME CONTRIBUTIONS OF ANESTHESIOLOGY TO THE GENERAL PRACTICE OF MEDICINE*

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ALMOST every physician, regardless of the type or medicine he practices, secretly believes that he has at least two other skills. He knows that he can deliver a baby and that he can administer anesthesia. He learned to do both in his senior year in medical school. If he could perform both tasks without mortality when he knew so little, why should he be concerned about the automatic maintenance of these abilities? Obstetricians have, by and large, ignored this implicit deprecation of their specialty, but anesthesiologists, younger as a group, have taken up cudgels in defense of their special interest in medicine. It appears timely, at long last, for anesthesiologists to abandon a hypersensitive attitude in trying to justify the existence of this field in medicine since its real contributions no longer require such self-conscious defenses.

Anesthesiology has grown in stature so that its proper and rightful place among the medical practices is assured. It makes little difference whether all other physicians think they can do almost as well. Men have also felt and some have even argued that the act of marriage itself can make them husbands and fathers. Most of us know better.

It appears evident, even on superficial consideration, that many physicians are totally unaware of the kind of knowledge that the anesthesiologist has at his command. The dissemination of this knowledge is a responsibility that anesthesiologists have not fulfilled adequately in the past. It is vitally necessary that serious efforts be made to inform physicians what is available in the care of patients as the result of lessons learned in the operating room, in the anesthesia laboratory and at the bedside of the patient. This body of knowledge is far from complete. In many ways it is quite inadequate to the tasks at hand. To say that much remains to be learned is not an unfavorable comment on the development of anesthesiology. It simply places this specialty in the ranks of all the others and points up the real satisfactions that are available to those whose interests include the search for new information in the fundamentals of medicine and for the anesthetic care of patients. This intellectual challenge is only evidence that many more good minds can aid in the furtherance of the progress of an intrinsically stimulating branch of medicine.

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It is the purpose of the present discussion to examine some of the current contributions of anesthesiology to the practice of medicine. To state this simply in sequence may be sufficient, but it is interesting to know some of the background concerned with the development of this knowledge. How, in other words, did the anesthesiologist break the fetters of the ether cone and emerge into the wider interests of medical practice from the roots of the operating room?

It is necessary to understand that the anesthesiologist did not and does not as a rule visit the home and consult with other physicians in that environment. It is the peculiar nature of this specialty that its growth and intellectual development have occurred in an institutional environment. This fact has not been a deterrent, but has been advantageous since it has screened the patient population in the sense of providing the most seriously ill people for study. Also, it must be granted that experience in a hospital cuts across almost all types of medical practice, another advantageous feature in versatility for the instruction of the physician, who spends almost all his time there. It may be a hard fact to accept for many of us, but the realities of the situation suggest that hospital experience is as valuable as any in medicine. The efforts of the American Academy of General Practice to obtain more hospital appointments for the general practitioner also support this thesis.

In the environment of the hospital, the anesthesiologist has become concerned with a surprising variety of problems in patient care. He has developed a large regular personal contact with patients in all the services in the institution. The problems that arise for the anesthesiologist are in part the result of his special skills and in part those which fall to his lot by default or the lack of more than cursory interest on the part of persons who are traditionally charged with such care. In this manner, the anesthesiologist who performs his duties properly has abandoned the role of the operating-room recluse, even though his major activities and interests are those of a member of the operating team. It is the experience in the operating room that has given him the skills that have been broadened to include many aspects of medical care in other situations.

The regular conduct of surgical anesthesia in daily activity is concerned with the use of some of the most potent and potentially the most dangerous of drugs employed in any type of medical practice. Anesthetic agents have unfavorable

pharmacologic effects on all the body systems, effects that present challenges in the restoration or at least approximate maintenance of normal physiologic activity. Although the undesirable changes, for example, of hepatic and renal function during almost all types of anesthesia are only beginning to come within the scope of understanding, the manifestations of abnormal respiration and circulation are comprehended sufficiently well to be of practical value in the therapy of similar states outside the operating room. Fortunately, much of this type of therapy is simple and can be utilized by all physicians without the need of special training in anesthesiology. This kind of information has not been disseminated adequately. It is almost painful to recollect the circumstances of an outstanding citizen in a community who had accidentally taken an excessive dose of barbiturates. He was found in his room, comatose and cyanotic with labored obstructed respiration. Several prominent physicians were called in consultation immediately. Epinephrine, Metrazol and Coramine were injected, to no avail. A useful life was lost because no physician present was aware in practical useful terms of the problem of the obstructed airway. The insertion of a pharyngeal airway is simple and lifesaving in such circumstances. In fact, even the introduction of a catheter into the trachea is not a difficult exercise if this should prove necessary to aspirate secretions from the tracheobronchial tree. Any physician who accepts patients whose illnesses include the possibility of asphyxia is obligated to master such methods or seek assistance from another who is qualified. Time is at a premium in effecting these measures.

Another respiratory-emergency lesson must be brought from the operating room to physicians in all forms of medical practice with constant and continuing force. This is the problem of apnea and depressed breathing, regardless of etiologic considerations. It is undoubtedly elementary but no less important to emphasize that it is of little consolation to permit a patient to die of asphyxia with a brilliant or even adequate diagnosis. The anesthesiologist has learned simply and sometimes sadly that depressed breathing during surgical anesthesia must be corrected promptly and efficiently if sudden death and crippling morbidity are to be minimized. There is only one method of dealing with asphyxia resulting from anesthesia, disease or injury, and that is the institution of efficient pulmonary ventilation through an open functional airway. In view of present knowledge, it is almost safe to insist on this concept as a dogma. Analeptic therapy and mutilating or brutal types of stimulation cannot be condoned as primary methods in the treatment of asphyxia. In the operating room it was learned many years ago that corrective therapy could be accomplished by inflation of the lungs with the aid of standard types of anesthesia apparatus. It was also discovered again and again that such time-honored practices as anal dilatation and thoracic-cage compression were grossly undependable. It is, of course, obvious that the physician cannot carry an anesthesia apparatus with him to the home. However, small, light and easily portable devices that can be used with a minimum of experience to perform adequate pulmonary ventilation — the only sure means of treating asphyxia — are available. One such device is illustrated in Figure 1. Awareness of proper pulmonary ventilation in treating asphyxiated patients and an effective means of implementation will save more lives than many of the other collected items in the physician's bag.

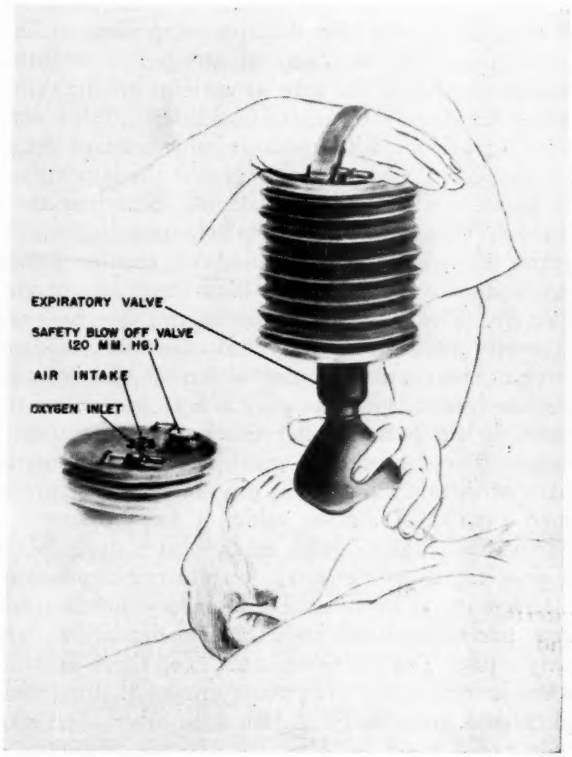

FIGURE 1. *Kreiselman Bellows Apparatus — a Simple Device for Artificial Respiration.*

A corollary of the problem of treating patients with anoxia or asphyxia is the practice of oxygen therapy. Unfortunately, much of oxygen therapy is becoming the province of technicians whose skills are real but nonetheless limited. It is not the present purpose to engage in an elaborate descriptive discussion of the details of oxygen therapy. There is one phase, however, that requires pointed emphasis because of the common neglect of an elementary principle of any type of drug therapy. To execute efficient therapy with oxygen it is necessary to ensure its access to pulmonary alveoli and

not merely to offer it to the patient's face. If the patient is breathing inadequately or through an obstructed airway, the degree of impaired ventilation is the determining factor in therapy and not the type of oxygen apparatus or the concentration of oxygen administered. Maximum advantage from oxygen inhalation can be gained only by adherence to the fundamental needs of adequate pulmonary ventilation.

The daily tasks of the anesthesiologist are so intimately and basically related to considerations of obtunding pain that it is not surprising to find him engaged in the study of analgesic modalities and drugs and in the care of patients with painful states unrelated to surgical operation. This constant experience with narcotic and sedative drugs has suggested to the anesthesiologist the importance of knowledge of analgesic agents, including their side effects, and has urged participation in the program of investigation planned to acquire better drugs and understand the older ones more adequately. The studies of Denton and Beecher[1] are examples of such activity. Because of frequent critical observation of the action of the opiates, the anesthesiologist has gained a great deal of respect for the potential harm to patients from their usage. These properties must become an integral part of the thinking of all physicians who employ such agents. Addiction aside, it has become apparent that analgesia effected by potent drugs bears a price tag in side effects. Respiratory depression, interference with normal circulatory homeostasis and gastrointestinal and urinary disabilities are only a few. The physician must keep these in mind when he employs these potent drugs. If drug complications are grossly undesirable, other means of pain relief must be sought. The anesthesiologist can offer some help in other methods as well.

Among the more widely available non-narcotic analgesic methods utilized in the therapy of painful states is procaine intravenously. The clinical reports indicate that this is an efficient analgesic procedure in the control of pain associated with the trauma of burns, fractures, sprains and surgical operations.[2-5] It has apparently been unsuccessful in the management of pain in cancer, neuritis and disabling arthritis. There is no generally accepted explanation for the mechanism of analgesia, although evidence has been presented in support of the thesis of central drug action.[6] It has also been suggested that analgesia is the result of leakage from the vascular bed and the consequent bathing of free nerve endings,[7] a hypothesis that is attractive but highly unlikely.[8]

A critical study of the evidence of the analgesic properties of intravenous administration of procaine leaves one with many doubts. The reports are striking in the absence of adequately controlled observations, although it is freely admitted that precision in the study of pain is most difficult. The difficulty lends emphasis to the need for improved methodology in the observation of analgesic agents in the treatment of painful states. It is readily apparent, nonetheless, that many patients who receive procaine intravenously experience relief of pain. The critical problem whether the favorable influence upon the pain syndrome was effected by procaine, psychic influences, spontaneous remission or inadequate definition of pain is as yet unanswered. These experiences have suggested to some that the study material is loaded with preconceived and erroneous impressions.

For example, it is generally agreed, with few exceptions, that pain is an integral part of surgical convalescence. These patients are frequently the subjects of study in evaluation of analgesic methods. In a study as yet unreported[9] it was found that satisfactory analgesia in postoperative patients could be achieved with intravenous administration of procaine in daily doses of 1 or 2 gm. as 0.1 per cent solution in approximately two thirds of the patients observed. This was most encouraging until it was demonstrated that the same degree of efficacy was possible with saline placebo solutions. It seems evident that there is a mistaken impression of the nature of post-surgical pain. The mistaken impression is easily transferred to the evaluation of a therapeutic agent. There is no intent in this discussion to suggest that intravenous administration of procaine is wholly without value. It may be a technic of importance, but the available evidence is far from conclusive. It is important to keep the realities in mind when this agent is used. The personality of the physician may be as integral a part of the therapy as the drug. Caution in interpretation of results is clearly indicated pending the development of better controlled studies.

The interest of the anesthesiologist in problems of pain has led to a considerable experience in the utilization of nerve-blocking methods. Many such procedures are available and valuable, but comment is reserved here for some that should be used frequently. This survey is by no means comprehensive.

The utilization of intercostal nerve block in the management of the pain associated with rib fracture is a valuable analgesic procedure from many points of view. The problem in this injury not only is one of analgesia but also represents the harmful systemic effects of pain in a vulnerable area of the body. Although it is perfectly true that simple uncomplicated rib fractures are not problems in pain control or in survival with a minimal morbidity, the same statement cannot be made of multiple rib fractures, which are frequently associated with intrathoracic complications. Pain in the latter situation not only is uncomfortable but also leads to impaired pulmonary ventilation, retention of secretions and the ravages of infection and anoxia. The relief of pain permits improved ventilation and

minimizes the potentiality of the morbid developments described. Pain relief obtained by immobilization or narcotic medication is attended by adverse effects on respiratory activity. Intercostal nerve block of the appropriate nerves, preferably by the paravertebral route, is an effective analgesic method that promotes rather than impedes respiration. Satisfactory pain relief, and consequently satisfactory ventilation, can be obtained with nerve block in more than 80 per cent of patients. A recent report of the experience gained in the treatment of more than 200 patients in this manner emphasizes the low mortality of 4.1 per cent.[10] The procedure itself was responsible for only a single death. This is a procedure well worthy of further application as a significant method of providing comfort and a better chance of survival after thoracic-wall injury. In this lesion, analgesia is the cornerstone of recovery with a minimum of complications.

Another relatively new and simple procedure is the performance of suprascapular nerve block.[11] The block depends upon specific anesthetization of the suprascapular nerve, which subserves sensation to the shoulder joint and its adjacent bursa. Suprascapular block is of symptomatic utility in the therapy of some cases of painful shoulder lesions. It appears to be most helpful in acute and intense subacromial bursitis and less efficacious in the therapy of chronic shoulder disabilities. Under no circumstance does suprascapular block replace definitive care of the shoulder lesion itself. It is to be regarded as a valuable analgesic tool to be used in conjunction with other direct measures in therapy.

An extremely interesting and provocative approach to the therapy of the somatic aspects of cardiac pain has recently been presented by Rinzler and Travell.[12] These observers have extended the initial observations of Weiss and Davis[13] on the therapy of visceral pain by local anesthesia of the somatic structures concerned in the perception of pain. The studies include the uncovering of the presence of zones of hypersensitivity or trigger areas in skeletal muscle. These trigger areas are in myofascial structures and produce a specific and characteristic reference of pain on pressure stimulation or needling. The pattern of reference is the same regardless of the activating cause of the trigger mechanism. The muscles involved in this phenomenon in coronary-artery disease are the pectoralis major and minor and the serratus anterior. It is essential that careful palpation of muscles be carried out to ascertain the precise location of these trigger areas. The technic consists of infiltration of the hyperalgesia zones with a few cubic centimeters of 0.25 per cent or 0.5 per cent procaine solution or spraying of the area with ethyl chloride. Best results are obtained in patients whose painful syndromes referred to somatic structures were precipitated by myocardial infarction. The least satisfactory effects were found in patients whose pain was a manifestation of angina of effort either without infarction or preceding this accident. Although the theoretical explanations for these effects are far from clear, Rinzler and Travell[12] emphasize the fact that this type of pain can be managed satisfactorily in the clinic by infiltration of the trigger zones.

Summary

The experiences of physicians in anesthesiology have been rewarding in many respects. In addition to the better care of patients subjected to operation, the anesthesiologist has learned medical disciplines that are useful in other spheres of medical practice. These include measures designed to combat asphyxia, circulatory depression and a variety of painful states. It is a matter of mutual responsibility that the general physician be aware of these potentialities for better patient care.

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SUBACUTE BACTERIAL ENDOCARDITIS CAUSED BY *GAFFKYA TETRAGENA**

Report of a Case

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GAFFKY[1] first described *Micrococcus tetragena*, now known as *Gaffkya tetragena*,[2] in 1881. Reimann,[3] in 1935, reported a case of septicemia and reviewed the literature. He found more than 170 cases of *G. tetragena* infections reported from other countries and 2 in the American literature. Subsequently, he reported extensive bacteriologic and immunological studies of this organism.[4-8] Since then, at least 6 cases of tetragena infections have been reported in this country, including septicemia, meningitis, pneumonia, penile ulcer and ulcerative stomatitis.[9-14] To date, in the entire literature, only 10 authenticated cases of subacute bacterial endocarditis caused by *G. tetragena* have been found.[15-20]

The following fatal case of subacute bacterial endocarditis is, to my knowledge, the second such case in the American literature and, since it was studied carefully, is considered worthy of report in some detail.

CASE REPORT

M. R., a 32-year-old auto mechanic, was admitted to Halloran Veterans Administration Hospital on April 23, 1948. He had presumably been well until March 30, when generalized weakness and aching in the shoulders developed. Within a few days, he experienced frequent chills and sweats. He was admitted to another hospital on April 12, where, during a 10-day stay, he ran a constant temperature elevation up to 102°F. accompanied by chills and sweats. Four blood cultures were reported as negative. He received penicillin intramuscularly every 3 hours for 5 days and streptomycin intramuscularly for 2 days. He was transferred to Halloran Veterans Administration Hospital with the tentative diagnosis of subacute bacterial endocarditis.

The patient recalled an episode of polyarthritis for which he had spent 2 months in bed at the age of 9 years. He had been told that he had a heart murmur at least 6 years preceding his present illness, but he denied any significant symptoms.

Physical examination showed that the patient was alert, in no acute distress and surprisingly well. A questionable petechia was found in the right lower conjunctiva. The lungs were clear, and there was a Grade II to III apical systolic murmur, which was transmitted to the left axilla and somewhat toward the base. The first mitral sound was loud and blunted. The pulse was dicrotic. The rate was regular at 80 per minute. The spleen was not felt. There were a few moderately enlarged, bilateral axillary and epitrochlear lymph nodes. The remainder of the examination was not remarkable.

Examination of the blood disclosed a red-cell count of 3,840,000, with a hemoglobin of 11.3 gm., and a white-cell count of 17,300, with 88 per cent neutrophils (19 stab forms), 10 per cent lymphocytes, 1 per cent monocytes and 1 per cent eosinophils. The urine was alkaline in reaction and gave negative results for sugar, protein, and on microscopical examination. The stools were negative for occult blood, ova, parasites and pathogenic organisms. The blood urea nitrogen was 11 mg. per 100 cc. The initial blood culture showed 380 colonies per cubic centimeter of a hemolytic, coagulase-negative organism of the micrococcus family. This organism was sensitive to 1.25 units of penicillin and to less than 4 units of streptomycin per cubic centimeter. It was resistant to all forms of sufonamides tested. X-ray examination of the chest revealed fibrous and fibrocalcific densities in both upper-lung fields that were considered typical of chronic pulmonary tuberculosis, probably inactive. An electrocardiogram showed a regular sinus rhythm, with right-axis deviation. A serologic test for syphilis was negative.

From the onset, the patient ran a febrile course, with temperatures spiking daily from 101 to 104°F. The pulse ranged from 80 to 100. Two days after admission, penicillin was started in a dosage of 100,000 units intramuscularly every 3 hours, and on the following day was increased to 200,000 units per dose. The patient's condition, however, remained unchanged. He complained of weakness, drowsiness, malaise and headache. On the night of the 5th hospital day, he had a convulsive seizure and lapsed into semicoma. By the following day he was in deep coma. Neurologic examination at that time showed a droop of the left eyelid, weakness of the right lower facial nerve, weakness of the right upper and lower extremities, hyperactive reflexes of the right upper extremity and absence of plantar responses. In the next few days, he gradually regained some semblance of consciousness in that he responded vaguely to various auditory and painful stimuli, and on several occasions he attempted to speak. Penicillin was discontinued on the 6th hospital day, and streptomycin was started in a dosage of 0.5 gm. every 6 hours intramuscularly. This was continued until the 17th hospital day. X-ray examination of the skull, mastoids and sinuses was negative. Lumbar puncture and ear, nose and throat examination were within normal limits. A ventriculogram on May 10 showed the left ventricle to be slightly larger than the right. Needle exploration did not reveal any intracranial abscess.

No major change was noted postoperatively. In time, definite petechiae appeared in the conjunctivas and retinas, and over the upper trunk and extremities. The apical systolic murmur gradually became more loud and harsh. The white-cell count remained elevated, varying from 12,000 to 22,000. The red-cell count gradually fell to 3,000,000, the hemoglobin reaching a final low of 7.4 gm. on June 11. There was no clinical response to several transfusions of whole, fresh blood.

Frequent blood cultures continued to show the same organism as was originally cultured. The colony count varied from 3 to over 800 per cubic centimeter but the majority were about 400 per cubic centimeter. The lowest colony count was found in one culture on May 18. Penicillin therapy was reinstituted on May 8, in the form of a continuous intravenous drip. By this route the patient received 10,000,000 units daily. This dosage was increased to 18,000,000 units per day, so that a total of 126,000,000 units was given in 7 days. During this time, the blood level of penicillin ranged from 15.0 to 39.9 units per cubic centimeter. In spite of this therapy, the resistance of the organism gradually increased until on June 1, it was resistant to more than 125 units of penicillin per cubic centimeter and also to more than 500 units of streptomycin per cubic centimeter. The use of antibiotics was stopped on May 25. The patient remained in coma and died quietly on the 51st hospital day and on the 76th day of his illness.

At autopsy the heart was not enlarged, weighing 300 gm. Old rheumatic valvular disease was evidenced by moderate thickening of the leaflets and thickening and slight fusion of the chordae tendineae of the mitral valve. In the patent, but valve-like foramen ovale, over the mitral valve and its chordae tendineae and on the central portion of the anterior leaflet of the pulmonary valve, there were many gray-yellow,

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friable, nodular vegetations varying in diameter from 0.5 to 1.5 cm. These vegetations were most abundant over the mitral valve (Fig. 1). Just above the bifurcation of the abdominal aorta, firmly attached to the intima, there was a firm, friable, red-brown mass. Similar but smaller masses were found within the right renal and splenic arteries. On section, these contained thick, creamy, yellow material. The spleen weighed 400 gm. and showed several red-brown infarcts. Many large, wedge-shaped, yellow-brown infarcts were found within both kidneys. The brain showed a large area of recent subarachnoid hemorrhage covering the right cerebral hemisphere. In the anterior horn of the left ventricle, between the putamen anteriorly and extending into the internal capsule posteriorly, there was an abscess measuring about 1 cm. in diameter. The lungs showed encapsulated, caseous, calcified foci in both upper lobes.

Microscopical examination of the heart disclosed an acute inflammatory reaction. This reaction was widespread, involving the myocardium, endocardium and valve leaflets. The leaflets of the mitral valve were extensively thickened and were covered by an outer layer of fibrin, within which there were large, purple-staining, granular, bacterial masses. The central portion of the valve leaflet was composed of a narrow zone of hyalinized connective tissue in which there were numerous capillaries, histiocytes and fibroblasts. The lesions within the kidneys, brain and abdominal aorta proved to be septic emboli, with abscess formation. Septic emboli were also found within the left coronary artery. An additional finding was an acute, focal, suppurative pancreatitis.

The organism found consistently in the blood culture was identified as *G. tetragena*. These studies will be reported elsewhere.[21] The same organism was isolated after death from the heart vegetations, aorta, brain and renal abscesses and from the various septic emboli.

Discussion

The historical background of childhood polyarthritis, the clinical knowledge of a "heart murmur" in adult life and the anatomic post-mortem findings of an old endocarditis established the diagnosis of rheumatic valvular heart disease. The superimposed bacterial infection (*G. tetragena*) of twelve weeks' duration confirmed the diagnosis of subacute bacterial endocarditis, according to the criteria outlined by Libman and Friedberg.[22]

From the clinical point of view, the case presented a number of interesting features. The relative well-being of the patient and the absence of toxic manifestations until relatively late in the course were especially striking in view of the persistently high bacterial count in the blood. This relative well-being coincides fairly well with the reports of other cases, especially those in the literature of other countries. It is of interest, in this respect, that *G. tetragena* has been accepted as being of very low virulence,[2, 23] and was originally described as non-pathogenic.[1] Of further interest is the behavior of this organism to antibiotics, with the extremely rapid development of resistance even in the face of massive doses of penicillin. Although no quantitative studies were done, the organism was noted to grow very freely in the presence of penicillin. The work of Paine and Finland[24] and that of Miller and Bohnhoff[25] on the facultative growth of certain organisms with streptomycin raise the possibility that a similar event played a part here. Pathologically, the widespread distribution of the septic infarcts and abscesses was noteworthy.

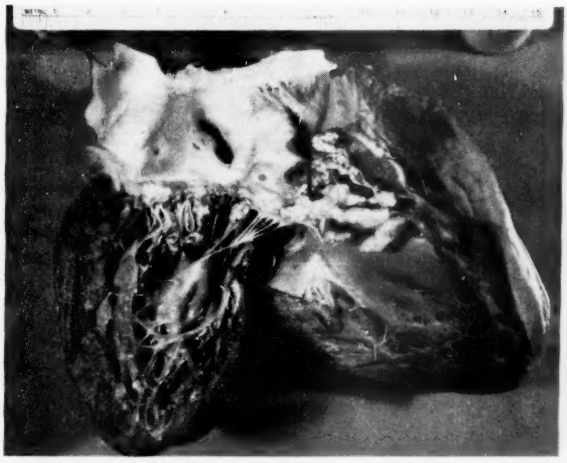

Figure 1. *Left Side of the Heart, Showing the Heavy Vegetations on the Mitral Valve and Chordae Tendineae.*

Summary

Clinical and autopsy findings in a case of subacute bacterial endocarditis caused by *Gaffkya tetragena* are reported.

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MEDICAL PROGRESS

THE EVALUATION OF CARDIOACTIVE AGENTS BY HUMAN BIOASSAY*

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RECENT advances in clinical research have demonstrated a new approach to the study of physiologic and pharmacologic problems. Until recently, most of the investigative work in these fields employed the laboratory animal as the test subject, and, although much valuable information has been gathered by these means, the investigators concerned have been the first to stress the fact that results so obtained should be accepted with caution, and to urge that suitable and safe methods be devised for the replacement of the laboratory animal by the human subject in clinical investigation.

During the past few years, many scientific tools have been developed, which have made possible the application of modified laboratory procedures to human subjects. Prominent among these are cardiac catheterization in the study of human cardiovascular dynamics and radioactive isotopes in the elucidation of human intermediary metabolism.

It is, in part, the purpose of this paper to outline a method, or series of methods, by means of which a similar result has been attained in pharmacologic research. It is of some importance that, since the studies described below originated in the middle 1920's, they antedate by a significant period the discovery of the more dramatic scientific weapons that are currently receiving close attention.

It will be readily perceived that the use of human material in pharmacologic study entails certain peculiar difficulties, and the investigations described below have proceeded under a clearly defined group of limitations that may be expressed somewhat as follows:

The determination of the clear-cut end point of death of the subject is obviously impossible. The concept of the lethal dose, so useful in animal work, has, of course, no place in human study. Provision must therefore be made for calculation of effects from end points that are not sharply defined.

The production of major toxic effects with experimental drugs is not permissible in human beings.

Surgical procedures, with direct observation and biochemical study of organs and tissues, cannot, of course, be utilized, as is often done in animal work.

When results are stated in terms of subjective sensations, such as relief of pain, the intrusion of psychic or emotional factors may play an important part in obscuring the findings.

Broadly speaking there are three methods by which these difficulties may be avoided: the use of indirect technics in the measurement of effects; the practice of carrying out large series of tests with mathematical and statistical treatment of results; and the use of the blind test.

Indirect Technics

Electrocardiogram

It is common knowledge that certain drugs that affect the cardiovascular system, notably members of the digitalis and cinchona groups, uniformly produce electrocardiographic changes. Advantage has been taken of these changes in the assay of members of the digitalis and cinchona series in human beings. Methods of electrocardiographic study have been devised for use in both regular sinus rhythm and auricular fibrillation.

In regular sinus rhythm, changes in the T wave are utilized as the basis for study. By a careful analysis of T-wave changes, a method for the bioassay of digitalis in man has been established by Gold and his co-workers.[1] An outline of their paper will serve to illustrate the procedure followed.

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Abridgment of a thesis submitted to McGill University Faculty of Medicine in partial fulfillment of the requirements for the diploma in internal medicine.

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The article describes a method for the practical assay of digitalis preparations in human beings by means of electrocardiographic changes. Ambulant patients having relatively normal electrocardiograms are selected. The control tracings should be fairly constant, and the T waves should be sensitive to 22 per cent change in dosage.

A three-point calibration of the patient is made with the standard preparation of digitalis. The doses differ by 22 per cent. Each dose is given after a control electrocardiogram. The effect of the dose of digitalis on the T wave is determined in an electrocardiogram taken twenty-four hours later. The unknown is compared with the standard in each of such calibrated subjects. The ratio of the dose

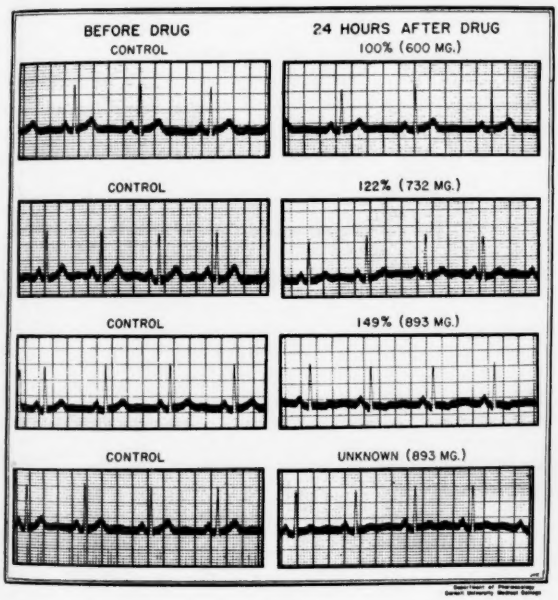


FIGURE 1. *Direct Assay of Digitalis Preparations in Man (Reproduced from Gold et al.,[1] with the Permission of the Publishers).*

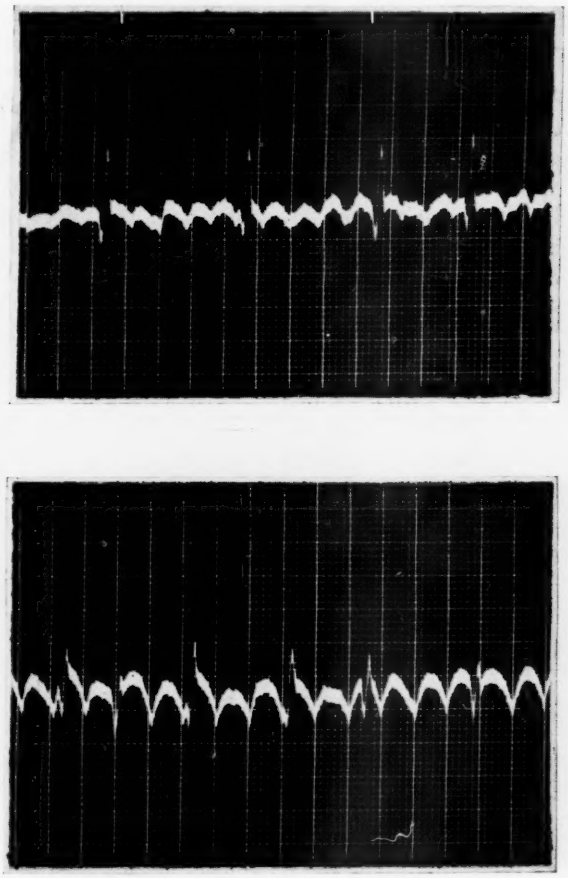
Subjects are selected in whom the T wave is a sensitive indicator of digitalis action. The response of the T wave is calibrated by graded doses of the standard (U.S.P. *reference powder*) *given at one-month intervals. In the case illustrated T-wave changes clearly distinguish 22 per cent difference in doses of the standard. It should be noted that 893 mg. of the unknown produces an effect between that of 732 and 893 mg. of the standard. Hence, the unknown has a potency approximating 812 mg., or 91 per cent of the standard.*

of the unknown that will produce a certain degree of effect to the dose of the standard that will produce the same effect represents the relative potency of the two preparations in a given subject. The average of these ratios in at least 6 subjects establishes the potency of the unknown in relation to the standard. Figure 1 illustrates the electrocardiographic changes utilized in this method of study.

By the use of this and similar methods, it has been possible to elucidate many important features of the pharmacology of digitalis, including information regarding digitalis cumulation,[2, 3] relative potencies of various digitalis preparations in animals and man[4, 5] and the salient fact that the results of animal bioassay are not transferable to man.

The electrocardiogram in auricular fibrillation has found its widest use in the study of the cinchona series. The methods used in such studies are very simple and produce a high yield of information. The procedure is carried out in the following manner:

BEFORE QUINIDINE



AFTER QUINIDINE

FIGURE 2. *Effect of Appropriate Oral Dose of a Cinchona Compound on the Electrocardiogram.*

Patients with auricular fibrillation are explored to determine which electrocardiographic leads produce readily measurable F waves. In most cases unconventional precordial leads are found to be the most useful. Selected patients are admitted to hospital, and, on the day of an experiment, breakfast is withheld and the patient is confined to bed. After a control electrocardiogram has been taken, the patient is given an oral dose of the cinchona salt to be tested. Electrocardiograms

are taken at two-hour intervals thereafter, for eight hours. Forty-eight hours usually elapse between doses, and the effects of doses of 0.1 to 2.0 gm. are usually tested. From 6-foot electrocardiographic strips, the average F-F interval is determined, and the average auricular rate calculated therefrom.

By the use of this method, the time of onset, duration and decline and disappearance of effect of oral doses of various cinchona salts[6, 7] and the relative potencies of various cinchona derivatives[8, 9] have been determined. These studies have also made it possible to recommend a rational dosage schedule for the quinidine therapy of various cardiac arrhythmias. Figure 2 illustrates the type of effect that is measured in these experiments. The difference in the length of the average F-F interval produced by an appropriate oral dose of a cinchona compound is graphically represented.

This discussion of the use of the F-F interval as an indicator of the effect of cinchona compounds on the heart barely outlines the subject. Enough has been said, however, to indicate clearly the wide potentialities of this scheme of investigation.

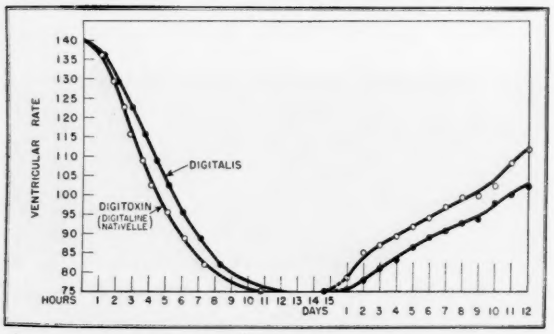


FIGURE 3. *Course of Action of Digitoxin Compared with that of Digitalis (Reproduced from Gold,[15] with the Permission of the Publishers).*

Each curve represents an average of heart-rate changes in several patients with auricular fibrillation after a single dose of the drug (3 cat units of digitoxin in 13 cases and 15 cat units in 30 cases). For therapeutically equivalent doses the speeds of absorption and elimination are approximately the same. In terms of cat units digitoxin has five times the potency of digitalis by oral administration in man.

Ventricular Rate in Auricular Fibrillation

Under carefully controlled conditions, studies of changes in the ventricular rate in patients with auricular fibrillation may be used as an accurate guide to the potency of various members of the digitalis series. The technic is unusually simple. Patients with this arrhythmia, and with rapid ventricular rates, are placed at bed rest, and their ventricular rates are counted at the apex several times daily until these rates have become stable. This usually requires about a week. On the morning of an experiment no food is given, and the ventricular rate is counted on several occasions to establish an average control figure. After this, a dose of the drug to be tested is given either orally or intravenously, and ventricular rates are counted at frequent intervals until the full effect of the drug has developed. Counts are then made at less frequent intervals over a period of twelve hours. In this way a complete curve of effect of the drug is obtained. This simple method has been used to classify many of the features of the cardiac action of the digitalis glycosides.[1-5, 10-19]

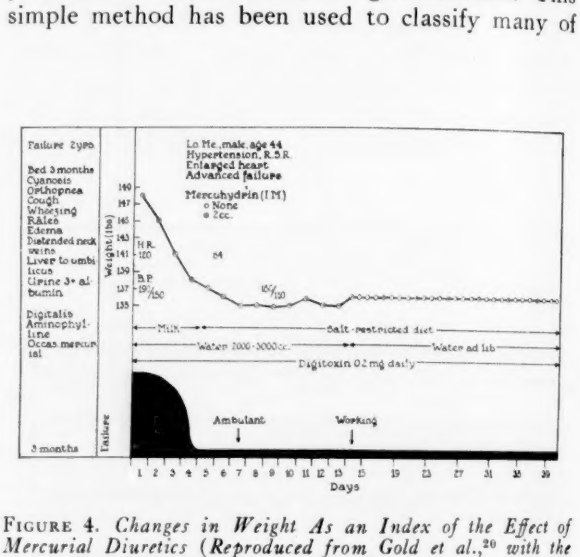


FIGURE 4. *Changes in Weight As an Index of the Effect of Mercurial Diuretics (Reproduced from Gold et al.,[20] with the Permission of the Publishers).*

An example of the results obtained in this type of study is shown in Figure 3, which indicates that the course of action of digitoxin is essentially the same as that of digitalis.

Weight Changes

A very striking illustration of the simplicity of these human bioassay methods in cardiovascular research is the employment of changes in weight as an index of the effect of mercurial diuretics. This has proved to be much more valuable than the time-honored intake-and-output method. One may even go so far as to say that the graph of the daily weights of a patient under treatment for congestive heart failure will closely approximate the general improvement in that patient's condition. Figure 4 shows such a daily weight chart superimposed on a graph representing severity of symptoms. Several quantitative observations on various mercurial diuretics[19, 21, 22] have been carried out, weight changes being used as the experimental end point. One such study[21] is described embodying a method for the quantitative comparison of Mercupurin and Mercuhydrin in ambulant patients with congestive heart failure.

The patient is weighed. He is then given a dose of the diuretic, and the effect is observed in terms of a loss of weight fifteen hours after the dose. This procedure may then be repeated as often as is necessary, in order to obtain a reliable average response to a given dose as a basis of comparison with another compound, tested in a similar manner, in the same subject.

Using weight changes as the standard in this study, the investigators were able to establish the fact that in the dose range of 1.0 and 2.0 cc., the diuretic responses to Mercupurin and Mercuhydrin by intramuscular and intravenous administration were indistinguishable. Employing the same standard, Modell, Gold and Clarke[22] demonstrated that the greatest sensitivity to Mercuhydrin for most patients with congestive heart failure lies in the range between 0.5 and 1.5 cc., and that the greatest clinical effects per unit weight of the drug may be expected from such doses.

It is perhaps desirable to emphasize again that these valuable additions to present-day knowledge regarding mercurial diuretics were made without the use of complicated laboratory procedures; that the studies here described were carried out on human subjects in a cardiac clinic; and that the simple expedient of weighing patients was the only diagnostic procedure used.

Drugs of Known Pharmacologic Effect as an Aid in the Study of Others

In pharmacologic studies on the laboratory animal, one of the common "tricks of the trade" involves the employment of a drug of known effect as an aid in the study of one whose effect is yet to be determined. This principle has been ingeniously adapted to human experiments in the study of pharmacology of digitalis by Gold and his coworkers. In a series of papers published from 1939 to 1941[23-25] the effects of digitalis, and modifications of those effects produced by atropine, were investigated in patients with auricular fibrillation.

The patients were given increasing doses of digitalis, which duly produced the expected fall in the ventricular rate. At the point of maximum effect produced by each dose, atropine, 2 mg. (1/30 gr.), was given intravenously, and the effect on the ventricular rate was noted. It was found that with small doses of digitalis, this amount of atropine blocked the ventricular slowing produced by the former drug. If the doses of digitalis were sufficiently large, atropine could *not* prevent digitalis from producing a marked slowing of a rapid ventricle.

From these findings, it is possible to make reasonable deductions concerning some features of the mechanism of digitalis action in auricular fibrillation. In digitalized patients with this arrhythmia the ventricle is maintained at a slow rate usually by the summation of two factors: a vagal factor, abolished by atropine, and an extravagal factor — probably a direct depression of the auriculoventricular node — not abolished by atropine. In the average case the vagal factor predominates after moderate doses and the extravagal factor predominates after large doses of digitalis. Which of the two factors has the greater influence, therefore, depends on the degree of digitalization (Fig. 5).

The clinical significance of these studies is obvious. It frequently occurs that patients with auricular fibrillation are digitalized at bed rest in the hospital with a satisfactory fall of the ventricular rate. On becoming ambulant these patients experience a significant rise in ventricular rate, which becomes even more exaggerated when mild or moderate physical exercise is undertaken. Recurrence of symptoms and of congestive heart failure may result. From these studies it is clear that such patients have been digitalized only to the degree at which the vagal effect is predominant; that exercise has stimulated reflex effects, resulting in the lifting of vagal tone; that further digitalization to the point of extravagal effect is indicated; and that this result can be achieved by an increase in the dose of digitalis.

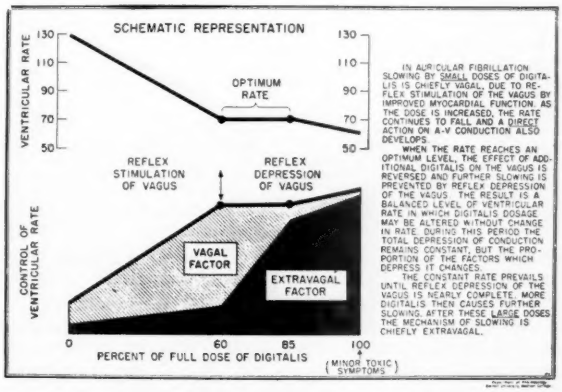

SCHEMATIC REPRESENTATION
VENTRICULAR RATE
130
110
90
70
50
OPTIMUM RATE
REFLEX STIMULATION OF VAGUS
REFLEX DEPRESSION OF VAGUS
CONTROL OF VENTRICULAR RATE
VAGAL FACTOR
EXTRAVAGAL FACTOR
0
60
85
100
PERCENT OF FULL DOSE OF DIGITALIS
(MINOR TOXIC SYMPTOMS)
IN AURICULAR FIBRILLATION SLOWING BY SMALL DOSES OF DIGITALIS IS CHIEFLY VAGAL, DUE TO REFLEX STIMULATION OF THE VAGUS BY IMPROVED MYOCARDIAL FUNCTION. AS THE DOSE IS INCREASED, THE RATE CONTINUES TO FALL AND A DIRECT ACTION ON A-V CONDUCTION ALSO DEVELOPS.
WHEN THE RATE REACHES AN OPTIMUM LEVEL, THE EFFECT OF ADDITIONAL DIGITALIS ON THE VAGUS IS REVERSED AND FURTHER SLOWING IS PREVENTED BY REFLEX DEPRESSION OF THE VAGUS. THE RESULT IS A BALANCED LEVEL OF VENTRICULAR RATE IN WHICH DIGITALIS DOSAGE MAY BE ALTERED WITHOUT CHANGE IN RATE. DURING THIS PERIOD THE TOTAL DEPRESSION OF CONDUCTION REMAINS CONSTANT, BUT THE PROPORTION OF THE FACTORS WHICH DEPRESS IT CHANGES.
THE CONSTANT RATE PREVAILS UNTIL REFLEX DEPRESSION OF THE VAGUS IS NEARLY COMPLETE. MORE DIGITALIS THEN CAUSES FURTHER SLOWING. AFTER THESE LARGE DOSES THE MECHANISM OF SLOWING IS CHIEFLY EXTRAVAGAL.

FIGURE 5. *Mechanism of Cardiac Slowing by Digitalis (Reproduced from Gold et al.,[24] with the Permission of the Publishers).*

In the investigations outlined above have described a simple, skillful application of a laboratory procedure to human study. It should be especially noted that this detailed and comprehensive elucidation of digitalis action was carried out with no more complex laboratory apparatus than a stethoscope, a few doses of atropine and a flight of stairs.

STATISTICAL TREATMENT

In the previous sections, indirect technics of pharmacologic study in the human subject have been described. It will probably have been noted that many of the standards utilized and the effects measured in these technics may lack sharp defini-

tion. Such a situation might readily detract from the validity of many of the conclusions drawn, were measures not taken to minimize the effect of the inaccuracies. It is the purpose of this section to describe the ingenious methods by which this problem is solved. Broadly speaking, the outstanding difficulty is avoided by the use of large numbers of subjects and the performance of mathematical and statistical analysis of the findings. The statistical results are expressed in the form of graphs,

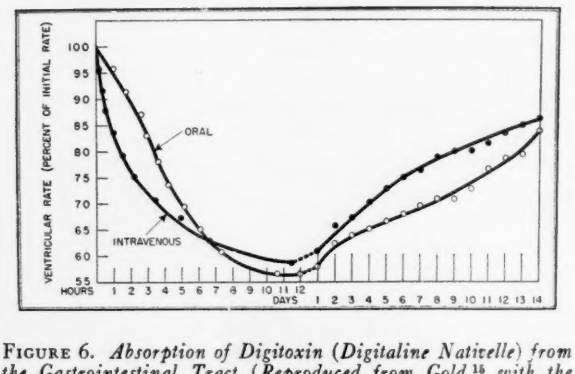


FIGURE 6. *Absorption of Digitoxin (Digitaline Nativelle) from the Gastrointestinal Tract (Reproduced from Gold,[15] with the Permission of the Publishers).*

The curves represent changes in ventricular rate in patients with auricular fibrillation. Each point represents on one curve the average of 13 cases after an oral dose of 1.25 mg. of digitoxin and on the other the average of 20 cases after a similar dose given intravenously. After the oral dose the rates decline from an average of 136 to 75 (61 beats); after the intravenous dose the decrease is from 140 to 82 (58 beats).

which include the curve of action, the dosage-response curve and the frequency-distribution curve.

Curve of Action

The most simple application of the curve of action is found in the graphic representation of the effect of a cardiac glycoside on the ventricular rate in auricular fibrillation. From such a graph in a single patient, information can be obtained about onset of effect, time of peak effect and elimination time of any cardiac glycoside.[14]

This simple procedure can be readily adapted to the production of composite curves of action (one drug — several patients); comparative action curves (one patient — several drugs); and curves of action that contrast the effect of equal oral and intravenous doses of the same preparation. The latter modification provides valuable information about the degree of absorption of cardioactive drugs from the gastrointestinal tract. The effect of an oral dose of digitoxin parallels almost exactly that of an intravenous dose (Fig. 6), thus indicating that digitoxin is almost completely absorbed from the gastrointestinal tract.

Dosage-Response Curve

The dosage-response curve is the result of a refinement of technic in the biologic assay of drugs. The preparation of such curves has been shown by Gold et al. to be an indispensable preliminary to the elucidation of the pharmacologic effect of any drug. The preparation of a dosage-response curve is, in its essence, an extremely simple procedure. It may be defined as a curve in which the magnitude of effect resulting from increasing doses of a drug is plotted against the doses that produced those effects. This method of treatment of biologic data may be applied to almost any type of response to almost any drug. In conjunction with the adop-

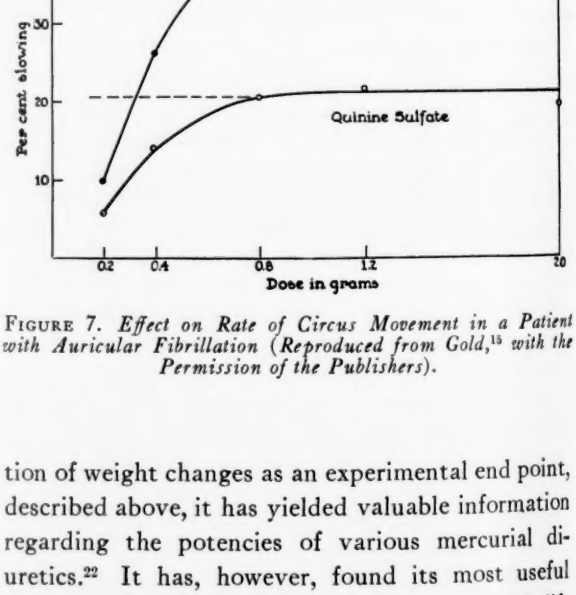


FIGURE 7. *Effect on Rate of Circus Movement in a Patient with Auricular Fibrillation (Reproduced from Gold,[15] with the Permission of the Publishers).*

tion of weight changes as an experimental end point, described above, it has yielded valuable information regarding the potencies of various mercurial diuretics.[22] It has, however, found its most useful application in the comparison of potencies of different cinchona compounds.[6-9] Figure 7 illustrates a pair of dosage-response curves prepared by plotting the percentage slowing of the auricles, produced by quinine sulfate and quinidine sulfate in auricular fibrillation, against the doses that brought about such slowing. It will be seen that these curves are sigmoid in shape — that is, they have ceilings. This indicates that an increase in the dose of the

drug beyond a certain point will not produce a parallel increase in the magnitude of effect, and that a state will finally be reached in which any increase in dose will no longer produce an increase in response. It will be recalled that this characteristic is common to many biologic phenomena, notably the dissociation curve of oxyhemoglobin; its general application in the field of pharmacology, however, has only recently been demonstrated.[6]

It is of some importance that the implications of the dosage-response curve be clearly understood. All cardioactive drugs so far studied by this method have exhibited ceiling effects, and it has been shown, for example, that different cinchona salts have ceilings of different heights, varying by as much as 100 per cent among themselves (Fig. 7).[6, 8, 9] Previous investigations of these alkaloids[26] had suggested that, although quinine and quinidine exhibited quantitative differences in their effects on auricular fibrillation, the dose of quinine could be increased to a level at which it would produce an effect equal to that of quinidine. Figure 7 shows, on the contrary, that, after a certain dosage level has been reached, quinine can no longer duplicate the magnitude of the effect produced by quinidine.

It should therefore be emphasized that the greatest sensitivity to most drugs lies in the range traced by the rising segment of the dosage-response curve, that the greatest clinical effect per unit weight of any drug may be expected from doses falling within this range, and that quantitative comparisons between drugs may become valueless if these facts are disregarded. The dosage-response curve is therefore the pharmacologic counterpart of the law of diminishing returns. It indicates that greater economy of drug and lesser incidence of toxic effects will be attained by the administration of doses that lie in the sensitive segment of the curve.

Frequency-Distribution Curve

The frequency-distribution curve is a statistical device that has found wide usage in the expression of various types of biologic measurements. The Price-Jones curve, for example, is a frequency-distribution curve expressing the variations in the diameters of normal red blood cells. In human pharmacologic studies it constitutes a method whereby wide sampling of the population may be substituted for sharp definition of effect. It may be recalled that a method was outlined above for the human assay of digitalis, in which the degree of lowering of the T wave of the electrocardiogram was the standard used for measuring the potency of a given specimen of digitalis. It may be justifiably argued that small changes in the T wave may easily fall within the limits of human or instrumental error, and that minor changes in the height of the T wave constitute unsatisfactory end points. This objection can be met satisfactorily by the application of the principle of the frequency-distribution curve. The technic may be outlined as follows:

A large number of patients — for example, 100 — with regular sinus rhythm are the subjects for this study. A control electrocardiogram is taken on each patient. A single oral dose of standard digitalis powder is then given. Twenty-four hours later a second electrocardiogram is taken. The same process is then repeated with each patient, graded doses of digitalis being administered until the full range of dosage (0.2 to 1.5 gm.) has been received by all patients. The electrocardiograms are then examined to determine which doses have produced any appreciable change in the T wave.

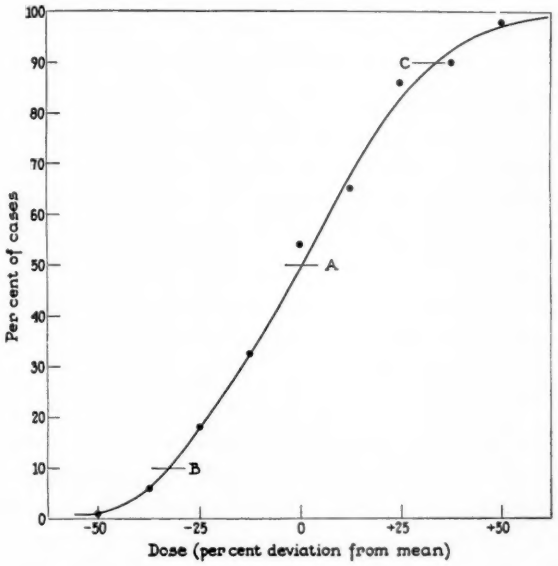


FIGURE 8. *Frequency-Distribution Curve of Digitalis Action by Oral Administration in Man (Reproduced from Gold,[15] with the Permission of the Publishers).*

It should be emphasized at this point that one does not seek to measure a series of gradations

in the magnitude of the T wave produced by a series of doses of digitalis in the same patient. One seeks, rather, to determine the number of subjects in which *any* T-wave change will be produced by a given dose of digitalis — in other words, how many patients out of 100 will exhibit T-wave changes in response to a 200-mg. dose of digitalis. One then determines how many patients out of 100 will exhibit T-wave changes in response to a 500-mg. dose, and so on, until doses of the drug up to 1500 mg. have been tested.

Using the data thus obtained, one may construct a frequency-distribution curve, in which the dose of digitalis is plotted against the percentage of the total number of patients in whose T waves variations have been produced. Figure 8 illustrates such a frequency-distribution curve of digitalis action in man, prepared by Gold and his associates.[27]

It will be observed that the mean dose of the standard digitalis powder produces T-wave changes in 50 per cent of the patients studied; that a dose of 25 per cent less than the mean produces T-wave changes in about 18 per cent of the cases; and that a dose of 25 per cent greater than the mean produces such changes in approximately 85 per cent of the cases.

With the information contained in this curve, the determination of the potency of an unknown specimen of digitalis is simple. To perform such an assay it is necessary only to administer orally a small dose of the unknown sample to a series of patients. The percentages of subjects in which this dose produces a change in the T wave is then determined. From the curve one can then ascertain which dose of the standard preparation would produce a T-wave change in the same percentage of cases, and the potency of the unknown with reference to the standard may thus be calculated.

It may be readily seen how this method for the human bioassay of digitalis may be applied to the determination of the potency of other drugs for which the results of varying doses are not susceptible of accurate measurement. It is safe to say that the principle of the frequency-distribution curve will probably be extended to include a wide group of biologic phenomena as yet untested by this method.

The Blind Test

As indicated above, the blind test finds its rightful place in human bioassay, in which results are stated in terms of subjective sensations, such as relief of pain, and in which the intrusion of psychic or emotional factors may play an important part in obscuring the findings. It is almost axiomatic that, given a state of affairs in which human observers study human subjects, human inaccuracies will creep in from both directions. The blind test is a mechanism for preventing human experimental error by the simple expedient of withholding certain information from both the observer and the subject. By this means, the factor of suggestion is denied to the patient in the reporting of his subjective sensations, and the knowledge of the expected action of a drug is prevented from exerting its influence upon the observer.

There are numerous methods by which this result may be obtained. Broadly speaking, however, these methods fall into such categories as the dispensing of different drugs for clinical trial in identical capsules; the arrangement of experiments in such a fashion that neither the experimenter nor the subject is informed of the nature of the drug administered or of the result to be expected; the ranking of electrocardiograms by cardiologists who are uninformed about which, if any drug, the patient has received; and the strictly impartial comparison of the effect of drugs with the presence or absence of effect of visually indistinguishable placebo preparations.[1, 6-9, 21, 27, 28] It is safe to say that the blind test has constituted a prime factor in the enhancement of the validity of experimental results that might otherwise be open to serious question.

By means of the series of procedures described above the emphasis in one branch of clinical research has been transferred from the laboratory animal to the human subject. In all cases an attempt has been made to illustrate and exemplify these methods from the rapidly increasing body of clinico-pharmacologic literature. In a certain number of the studies quoted, I have been an active participant.[7, 9, 12] It will not escape notice that the bibliography consists almost entirely of papers emanating from one laboratory — a feature for which no apologies are necessary, since clinical pharmacology

had its inception in the work of and continues to draw its chief stimulus from Gold and his collaborators.

Summary

A series of procedures are described for the human bioassay of certain cardioactive drugs.

These procedures include the use of indirect technics for the measurement of results; the practice of carrying out large series of tests with statistical treatment of findings; and the use of the blind test to neutralize the effect of psychic and emotional factors.

The indirect technics employed include the electrocardiogram in regular sinus rhythm and in auricular fibrillation; the ventricular rate — observations of changes in patients with auricular fibrillation; weight changes — in the study of diuretics, mercurial and otherwise; and the use of drugs of known pharmacologic effect in the study of other drugs, whose mechanism of action has yet to be determined.

The methods for statistical treatment of results include the curve of action, the dosage-response curve and the frequency-distribution curve.

I am indebted to Dr. Harry Gold, professor of clinical pharmacology, Cornell University Medical College, for his kind interest and helpful advice in the preparation of this paper, and for permission to use material and illustrations contained therein.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor* BENJAMIN CASTLEMAN, M.D., *Associate Editor*
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NORMAL LABORATORY VALUES

To provide ready reference to the normal values of laboratory procedures* recorded in the "Case Records of the Massachusetts General Hospital" and to the methods used the tabular summary† originally published in January, 1946, has been revised and is substituted for one of the cases. A limited number of reprints will be available and will be forwarded, so long as the supply lasts, provided a self-addressed stamped envelope (approximately 4 by 9 inches) accompanies the request, which should be addressed to Miss Virginia W. Towne, Massachusetts General Hospital, Boston 14.

* * *

Blood, Plasma or Serum Values

DETERMINATION	NORMAL VALUE	MATERIAL ANALYZED	MINIMUM QUANTITY REQUIRED‡	NOTE	METHOD
			cc.		
Amylase	15–45 units per 100 cc.	Serum	5	Do not draw during or just following intravenous glucose	Adapted from Somogyi: *J. Biol. Chem.* **125**:399, 1938
	8–18 Russell units per 100 cc.	Serum	5	Done only when blood sugar is elevated; also done on bile or duodenal drainage.	Huggins and Russell: *Ann. Surg.* **128**:668, 1948
Ascorbic acid (vitamin C)	0.4–1.0 mg. per 100 cc.	Serum	2		Butler, Cushman and MacLachlan: *J. Biol. Chem.* **150**:453, 1943
	0.4–1.5 mg. per 100 cc.	Blood	7	Use special heparin bottle	Roe and Kuether: *J. Biol. Chem.* **147**:399, 1943
Bilirubin (van den Bergh test)	Direct: 0.4 mg. per 100 cc. Total: 0.7 mg. per 100 cc.	Serum	5	Total is water and alcohol-soluble bilirubin (miscalled indirect)	Malloy and Evelyn: *J. Biol. Chem.* **119**:481, 1937
Bromide	0	Serum	5	—	Adapted for photoelectric colorimeter from Wuth: *J. A. M. A.* **88**:201, 1927
Calcium	8.5–10.2 mg.§ per 100 cc. (4.2–5.1 milliequiv. per liter)	Serum	5	Take fasting; as value given is a total calcium, serum protein should be ordered also.	Fiske and Logan: *J. Biol. Chem.* **93**:211, 1931 Folin: *Lab. Manual Biol. Chem.*, 5th ed., p. 351
Carbon dioxide (content)	26–28 milliequiv. per liter (20–26 milliequiv. per liter in infants and children)	Serum	3	Draw without stasis under oil; milliequiv. per liter equals volumes per cent divided by 2.2; the milliequiv. total CO_2 minus 1.3 is usually equal to the HCO_3 expressed as milliequiv. per liter.	Van Slyke and Neill: *J. Biol. Chem.* **61**:523, 1924 Peters and Van Slyke: *Quant. Clin. Chem.*, Vol. II, p. 283
Carotenoids: Total	1–3 int. units per cc.	Serum	5	Carotenoids and vitamin A done on same sample	Josephs: *Bull. Johns Hopkins Hosp.* **65**:112, 1939 (modified for photocolorimeter and calibrated with haliver oil of specified vitamin A content)
Vitamin A	0.4–1 int. unit per cc.	Serum			
Chloride	100–106 milliequiv. per liter	Serum	2	—	Wilson and Ball: *J. Biol. Chem.* **79**:221, 1928

*The chemical data were prepared by G. Margaret Rourke, chief of the Chemical Laboratory, Elsie A. MacLachlan, consultant, and Allan M. Butler, staff physician in charge of the Chemical Laboratory.

†Normal laboratory values. *New Eng. J. Med.* **234**:24-28, 1946.

‡Minimum quantity refers to amount of whole blood required for a single analysis unless otherwise stated. It is imperative that a dry syringe and needle be used in collecting samples since hemolysis invalidates many tests.

§1 milliequiv. equals the molecular weight of the element in milligrams divided by the valence of the element.

Determination	Normal Value	Material Analyzed	Minimum Quantity Required‡	Note	Method
			cc.		
Cholesterol	150–280 mg. per 100 cc.	Serum	3	Cholesterol and cholesterol esters done on same sample	Bloor: *J. Biol. Chem.* **24**: 227, 1916
Cholesterol esters	45–65 per cent of total cholesterol	Serum	3		Bloor and Knudson: *J. Biol. Chem.* **27**:107, 1916
Creatinine	0.7–1.7 mg. per 100 cc.	Serum	5	—	Peters: *J. Biol. Chem.* **146**: 179, 1942
Fatty acids	190–420 mg. per 100 cc.	Serum	12	—	Stoddard and Drury: *J. Biol. Chem.* **84**:741, 1929
Fibrinogen	0.15–0.30 gm. per 100 cc.	Plasma	2	Collect in graduated prothrombin tubes as for prothrombin time	Cullen and Van Slyke: *J. Biol. Chem.* **41**:587, 1920
Glucose	70–100 mg. per 100 cc.	Blood	0.5	Use oxalate-fluoride bottles or microsugar tubes and special pipettes	Folin: *Lab. Manual Biol. Chem.*, 5th ed., p. 507 Folin: *New Eng. J. Med.* **206**:727, 1932
Hemoglobin	14–16 gm. per 100 cc.	Blood	0.02	Oxalated blood may be used, or freshly drawn blood may be put into solution on ward	Evelyn: *J. Biol. Chem.* **115**: 63, 1936
Iodine	3.5–7.5 microgm. per 100 cc.	Serum	12	Draw under oil	Barker: *J. Biol. Chem.* **173**: 715, 1948
Iron	125–280 microgm. per 100 cc.	Serum	12	—	Schales's unpublished method, contained in Klett–Summerson Handbook (adapted to Evelyn photocolorimeter)
Lactic acid	2–20 mg. per 100 cc.	Blood	2	Use special bottles	Barker and Summerson: *J. Biol. Chem.* **138**:535, 1941
Lipase	Under 2 cc. (0.05N NaOH)	Serum	5	Entails a 24-hr. incubation period	Comfort and Osterberg: *J. Lab. & Clin. Med.* **20**:271, 1934–35
Magnesium	1.5–2.5 milliequiv. per liter	Serum	5	—	Garner: *Biochem. J.* **40**:828, 1946
Nonprotein nitrogen	15–35 mg. per 100 cc.	Serum	3	May also be done on whole blood; normal value slightly higher (up to 40 mg. per 100 cc.).	Folin: *Lab. Manual Biol. Chem.*, 5th ed., p. 265
Oxygen:					
Capacity	19–22 vol. per cent	Blood	3	Obtain special tubes containing oxalate, oil and stirring rod from chemistry laboratory	Van Slyke and Neill: *J. Biol. Chem.* **61**:523, 1924 Peters and Van Slyke: *Quant. Clin. Chem.*, Vol. II, p. 321
Arterial content	18–21 vol. per cent	Blood	3		
Arterial percentage saturation	94–96 per cent				Arterial content divided by arterial capacity
pH (reaction)	7.35–7.45	Serum	2	Draw without stasis and under oil; pack in ice and send to laboratory at once.	Hastings and Sendroy: *J. Biol. Chem.* **61**:695, 1924 Peters and Van Slyke: *Quant. Clin. Chem.*, Vol. II, p. 796
Phosphatase, acid	0.5–2.0 units per 100 cc.	Serum	4	Must be drawn just prior to analysis	Gutman and Gutman: *J. Biol. Chem.* **136**:201, 1940
Phosphatase, alkaline	2.0–4.5 units per 100 cc. About 14 units per 100 cc. (infants) About 5 units per 100 cc. (adolescents)	Serum	3	Value parallels rate of growth	Bodansky: *J. Biol. Chem.* **101**:93, 1933 (using method for determining inorganic phosphorus)
Phosphorus, inorganic	3.0–4.5 mg. per 100 cc.	Serum	1	Must be taken fasting; in newborn infant values as high as 6 mg. per 100 cc. that diminish during first year; in childhood values approach normal adult average.	Fiske and Subbarow: *J. Biol. Chem.* **66**:375, 1925 Folin: *Lab. Manual Biol. Chem.*, 5th ed., p. 341 (modified for photocolorimeter)

‡Minimum quantity refers to amount of whole blood required for a single analysis unless otherwise stated.

Determination	Normal Value	Material Analyzed	Minimum Quantity Required‡ cc.	Note	Method
Phospholipids	12–14 mg. per 100 cc. as P	Serum	3	Place immediately in refrigerator	Bloor: *J. Biol. Chem.* **36**:33, 1918; Fiske and Subbarow: *J. Biol. Chem.* **66**:2, 1925
Potassium	3.5–5.0 milliequiv. per liter	Serum	2 (flame) 10 (chemical)	Must not stand on cells more than 1 hr. Flame photometer used routinely	Berry, Chappell and Barnes: *Indust. & Engin. Chem.* **18**:19, 1946; Fiske and Litarczek in Folin: *Lab. Manual Biol. Chem.*, 5th ed., p. 353
Protein:					
Total	6.0–8.0 gm. per 100 cc.	Serum	1 (micro)	All albumin-globulin ratios require a macro-protein for total protein and albumin and also a non-protein nitrogen; globulin calculated by difference.	Macro: Peters and Van Slyke: *Quant. Clin. Chem.* Vol. II (Methods) p. 691
Albumin	4.5–5.5 gm. per 100 cc.	Serum	5		Micro: Lowry and Hastings: *J. Biol. Chem.* **143**:257, 1947
Globulin	1.5–3.0 gm. per 100 cc.	Serum			
Prothrombin time	Given with each analysis	Plasma	2	Obtain special oxalate tubes from laboratory; collect blood with extreme care and send to laboratory at once.	Quick: *J. A. M. A.* **110**: 1658, 1938
Salicylate	0	Serum	5	—	Killer: *Am. J. Clin. Path.* **17**:415, 1947
Sodium	136–145 milliequiv. per liter	Serum	3	—	Butler and Tuthill: *J. Biol. Chem.* **93**:171, 1931
Sulfonamides	0	Blood	2	Reported as "free" or unconjugate form of drug; if presence of conjugate form is suspected, total should be ordered.	Bratton and Marshall: *J. Biol. Chem.* **128**:537, 1939
Thiocyanate	Under 1 mg. per 100 cc.	Serum	3	—	Griffith and Lindauer: *Am. Heart J.* **14**:710, 1937
Urea nitrogen	10–28 mg. per 100 cc.	Serum	3	—	Van Slyke: *J. Biol. Chem.* **73**:695, 1927 Peters and Van Slyke: *Quant. Clin. Chem.*, Vol. II, p. 372
Uric acid	3–5.5 mg. per 100 cc.	Serum	3	—	Folin: *J. Biol. Chem.* **101**: 111, 1933

‡Minimum quantity refers to amount of whole blood required for a single analysis unless otherwise stated.

Cerebrospinal-Fluid Values

Determination	Normal Value	Minimum Quantity Required cc.	Note	Method
Initial pressure	70–180 mm. of water	—	—	—
Cell count	0–5 mononuclear cells (lymphocytes)	0.2	—	—
Chloride	120–130 milliequiv. per liter	0.5	—	Same as that for serum (see above)
Protein				
Method I	15–45 mg. per 100 cc.	1	Protein done by both methods whenever there is sufficient spinal fluid	Ayer, Dailey and Fremont-Smith: *Arch. Neurol. & Psychiat.* **26**:1038, 1931
Method II (photo)	15–45 mg. per 100 cc.	1		Method I adapted to photoelectric colorimeter
Glucose	50–75 mg. per 100 cc.	0.1	—	Same as that for blood (see above)
Colloidal gold	0000000000	0.1	—	Wuth and Faupel: *Bull. Johns Hopkins Hosp.* **40**:297, 1927

Urine Values

Determination	Normal Value	Minimum Quantity Required	Note	Method
		cc.		
Albumin (quantitative)	0	3	Preserve with toluol or chloroform and keep in refrigerator	Peters and Van Slyke: *Quant. Clin. Chem.*, Vol. II, p. 691
Ammonia	20–70 milliequiv. per liter	24-hr. specimen	Collect under toluol and keep in refrigerator	Van Slyke and Cullen: *J. Biol. Chem.* **24**:117, 1916
Barbiturates	0	100–200 cc.	May also be done on stomach washings	Simmons and Gentzkow: *Lab. Methods of U. S. Army*, p. 327
Calcium	Under 150 mg. of total output	24-hr. specimen	Patient must be on low-calcium diet	Same as that for serum (see above)
Creatine	Under 100 mg. of total output	24-hr. specimen	Preserve with toluol or chloroform and keep in refrigerator	Folin: *Lab. Manual Biol. Chem.*, 5th ed., p. 163
Creatinine	15–25 mg. per kg. of body weight	24-hr. specimen	Preserve with toluol or chloroform and keep in refrigerator	Folin: *Lab. Manual Biol. Chem.*, 5th ed., p. 159 (modified for photocolorimeter)
Diastase	Dilution of 1:4 to 1:16	2	Sample must be freshly drawn	Stitt: *Pract. Bact., Haem. & Parasitol.* 9th ed., p. 731
Follicle-stimulating hormone (FSH)	Before puberty, less than 6.5 mouse units per 24 hr.; after puberty 6.5–52 mouse units per 24 hr.; after menopause, 96–600 mouse units per 24 hr.	24-hr. specimen	—	Klinefelter, Albright and Griswold: *J. Clin. Endocrinol.* **3**:529, 1943
17-ketosteroids	Under 8 yr., 0–2 mg. per 24 hr.; adolescents, 2–20 mg. per 24 hr.; males, 8–20 mg. per 24 hr.; females, 5–14 mg. per 24 hr.	24-hr. specimen	—	Talbot, Butler, MacLachlan and Jones: *J. Biol. Chem.* **136**:365, 1940; Fraser, Forbes, Albright, Sulkowitch and Reifenstein: *J. Clin. Endocrinol.* **1**:234, 1941
11-oxy-ketosteroids	0.06–0.2 mg. per 24 hr., per sq. meter of body surface (adults, 0.1–0.4 mg. per 24 hr.)	24-hr. specimen	—	Talbot, Albright, Saltzman, Zygmuntowicz and Wixom: *J. Clin. Endocrinol.* **7**:331, 1947
Sugar:			Collect samples for sugar under toluol and keep in refrigerator	
Total (quantitative)	0	20		Benedict: *J. A. M. A.* **57**: 1193, 1911
Fermentable	0	5		Hawk and Bergheim: *Pract. Physiol. Chem.* 10th ed., p. 750
Fructose	0	5		Hawk and Bergheim: *Pract. Physiol. Chem.* 10th ed., p. 772
Galactose or lactose	0	6	—	Total sugar minus fermentable sugar x 1.24
Osazone, difference of	0	5	—	Hawk and Bergheim: *Pract. Physiol. Chem.* 10th ed., p. 50
Urobilinogen	1.0 Ehrlich unit (total in 2 hr.)	2-hr. sample (1–3 p.m.)	—	Watson, Schwartz, Sborov and Bertie: *Am. J. Clin. Path.* **15**:605, 1944

Liver-Function Tests

Determination	Normal Value	Amount Administered	Material Analyzed	Minimum Quantity Required‡	Note	Method
				cc.		
Bromsulfalein	Less than 5 per cent retention	2 mg. per kg. intravenously	Serum (30 min. after injection)	5	Used in patients with slight jaundice	Rosenthal and White: *J. A. M. A.* **84**:1112, 1925; Photo.: Goebler: *Am. J. Clin. Path.* **15**:452, 1945
	Less than 5 per cent retention	5 mg. per kg. intravenously	Serum (45 min. after injection)	5	Used in patients without jaundice (bromsulfalein test is valueless in patients with obvious jaundice)	*Ibid.* (modified, *i.e.*, result ÷ 2.5) (both methods used whenever there is sufficient serum)
Cephalin flocculation	Up to ++ in 48 hr.	0	Serum	1	—	Hanger: *J. Clin. Investigation* **18**:261, 1939
Galactose tolerance	Less than 5 mg. per 100 cc. at 75 min.	0.5 gm. per kg. intravenously	Blood	2	Fluoride must *not* be used in anticoagulant	Basset, Althausen and Coltrin: *Am. J. Digest. Dis. & Nutrition* **8**:432, 1941
Hippuric acid	Greater than 1 gm.	1.77 gm. sodium benzoate intravenously	Urine	1-hr. sample	—	Quick, Ottenstein and Weltchek: *Proc. Soc. Exper. Biol. & Med.* **38**:77, 1938; Moser, Rosenak and Hasterlik: *Am. J. Digest. Dis. & Nutrition* **9**:183, 1942
Thymol flocculation	Up to + in 24 hr.	0	Serum	1	—	MacLagen: *Nature* **154**:670, 1944 (modified for photoelectric colorimeter)
Thymol turbidity	0–4 units per 100 cc.	0	Serum	1	—	MacLagen: *Nature* **154**:670, 1944 (modified for photoelectric colorimeter)
Urobilinogen	Up to 1.0 Ehrlich units total per 2-hr. specimen	0	Urine	1–3 p.m. specimen	—	Same as that for urine (see above)
Volume of blood (total)	8.5–9 per cent of body weight in kg.	Exactly 10 cc. of 0.1 per cent T1824 (Evans blue) in saline intravenously	Serum (before and 5, 10 and 15 min. after injection)	3 (each sample)	Note exact time after injection each sample is withdrawn; use calibrated syringe; patient must be fasting.	Gregerson and Stewart: *Am. J. Physiol.* **125**:142, 1939

‡Minimum quantity refers to amount of whole blood required for a single analysis unless otherwise stated.

Renal-Function Tests

Determination	Normal Value	Amount Administered	Material Analyzed	Minimum Quantity Required‡	Method
				cc.	
Phenolsulfonphthalein	25 per cent or more in first 15 min.; 40 per cent or more in 30 min.; 55 per cent or more in 2 hr.	1 cc. intravenously	Urine	Total output	Chapman: *New Eng. J. Med.* **214**:16, 1936
Urea clearance	75 to 125 per cent of normal	0	Blood and urine	Blood, 6 cc.; urine, two 1-hr. samples	Peters and Van Slyke: *Quant. Clin. Chem.*, Vol. II (Methods), p. 564

‡Minimum quantity refers to amount of whole blood required for a single analysis unless otherwise stated.

Hematologic Values

Determination	Normal Value	Minimum Quantity Required‡ cc.	Note	Method
Bleeding time	Below 4½ min.	—	—	Duke: *J. A. M. A.* **55**:1185, 1910
Clotting time	Below 20 min.	20	—	Lee and White in Todd and Sanford: *Clin. Diag. by Lab. Methods*, 10th ed., p. 199
Fragility of red cells	No hemolysis in 0.5 per cent sodium chloride	5	—	Hunter: *J. Clin. Investigation* **19**:691, 1940
Sedimentation rate	Less than 0.35 mm. per min.	5	Heparin used as anticoagulant	Rourke and Ernstene: *J. Clin. Investigation* **8**:545, 1930
	Less than 15 mm. per hr.	5	Internal diameter of tube should be 4 mm. instead of 2.5 mm.	Modification of Wintrobe and Landsberg: *Am. J. M. Sc.* **189**:102, 1935
Hematocrit (percentage volume of packed red cells)	Males, 42–50 per cent; females, 40–48 per cent.	2	—	*Ibid.*
Hemoglobin	14–16 gm. per 100 cc.	0.05	—	Evelyn: *J. Biol. Chem.* **115**: 63, 1936
Mean corpuscular volume	80–94 cu. microns	—	—	(Hematocrit x 10) ÷ red cells (in millions)
Mean corpuscular hemoglobin	27–32 micromicrogm.	—	—	(Gm. of hemoglobin x 10) ÷ red cells (in millions)
Mean corpuscular hemoglobin concentration	33–38 per cent	—	—	(Gm. of hemoglobin x 100) ÷ hematocrit

‡Minimum quantity refers to amount of whole blood required for a single analysis unless otherwise stated.

Miscellaneous Values

Determination	Normal Value	Material Analyzed	Minimum Quantity Required‡ cc.	Note	Method
Stool fat	4 per cent of fat intake per day	Stool	3-day specimen	Record fat intake while stool is being collected; sample used in determination must be homogeneous.	Fowweather: *Brit. J. Exper. Path.* **7**:7, 1928
Stool nitrogen (total)	0.8–2.0 gm. per 24 hr.	Stool	3-day specimen	—	Peters and Van Slyke: *Quant. Clin. Chem.*, Vol. II (Methods), p. 353
Calculi	—	—	Representative sample	—	McIntosh and Salter: *J. Clin. Investigation* **21**: 751, 1942
Congo red test	More than 60 per cent retention in serum after 1 hr.	Serum	6 cc.	Patient must be fasting; give 20 cc. of 1 per cent Congo red; draw a 4-min. and 60-min. sample from opposite arm.	Bennhold: *Deutsches Arch. f. klin. Med.* **142**:32, 1923

‡Minimum quantity refers to amount of whole blood required for a single analysis unless otherwise stated.

CASE 36451

Presentation of Case

A fifty-three-year-old woman entered the hospital complaining of lack of energy, a slight cough and pain at the base of the left chest.

She was well until two and a half years before entry, when, while abroad, she had an attack of pneumonia. The radiologic diagnosis was pneumonia of the left lower lobe. The patient was acutely ill, but because of inadequate hospital facilities she was treated at home with sulfonamides and penicillin. The sulfonamides were stopped however because of a low blood count. She recovered in three months. By x-ray examination a shadow persisted in the left lung, and the hilar lymph nodes were prominent. This was diagnosed radiologically as inflammatory disease of the lingula of the left upper lobe. Bronchoscopy showed narrowing of the lower bronchus. Repeated examinations of the sputum for tuberculosis were negative. Tomography performed six months later was reported as showing atelectasis of the lingula of the left upper lobe. Radiologic examinations of the chest at six-month-intervals revealed no change in the lesion. Three months before entry the patient again developed a respiratory infection. She felt unusually tired and developed a dry cough occasionally productive of mucoid sputum. There was no hemoptysis. She complained of a constant, dull aching pain at the base of the left chest and slight shortness of breath on exertion. She had lost 30 pounds in the past three months.

She had had moderately high blood pressure for many years, with morning headaches and occasional attacks of spontaneous epistaxis. She had a bilateral saphenous-vein ligation six years prior to entry.

Physical examination revealed an alert, cooperative woman in no acute distress. Coarse, moist rales and diminished whispered voice sounds were heard over the left upper chest. The examination was otherwise negative.

The temperature, pulse and respirations were normal. The blood pressure was 185 systolic, 75 diastolic.

Examination of the blood showed a hemoglobin of 12.0 gm. and a white-cell count of 8300, with 63 per cent neutrophils, 32 per cent lymphocytes, 4 per cent monocytes and 1 per cent basophils. Cytologic examination of the sputum was negative for tumor cells, and a smear disclosed no tubercle bacilli. A urinalysis was negative. Radiologic examination of the chest with bronchograms revealed a hazy homogeneous density throughout the distribution of the lingula of the left upper lobe, with calcified nodes at the expected point of origin of the bronchus to the lingula and a discrete calcification in the left lower lobe laterally (Fig. 1). The lung fields were otherwise normal, and comparison with previous films failed to show any change in the lesion.

On the sixth hospital day an operation was performed.

Differential Diagnosis

Dr. Thomas Gephart*: In summation this fifty-three-year-old woman had had disease in the left chest for at least two and a half years.

Dr. Wyman, may we look at the x-ray films?

Dr. Stanley M. Wyman: This lesion overlies the left heart border and is almost triangular in shape. It is well identified in the lateral view, lying

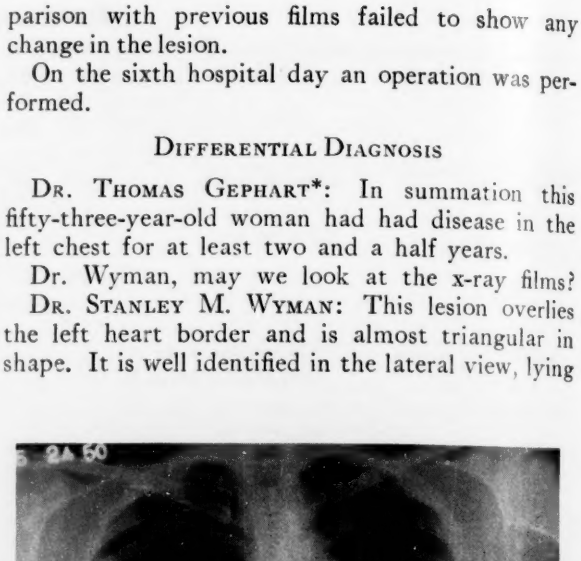

Figure 1.

far anteriorly and again overlying the heart border. There are several mottled calcifications at the site of the expected origin of the lingular bronchus of the left upper lobe, which are best seen on the grid film. These can also be seen in the lateral film lying in the hilus at the apex of the triangular density of the diseased lingula. The discrete calcification described in the protocol in the lower lobe is seen to be entirely separate and is consistent with a healed Ghon complex.

Dr. Gephart: I gather from the report of the bronchograms that there was no filling?

Dr. Wyman: That is correct.

Dr. Gephart: In the report of one bronchoscopy that was apparently done about two years previously, there was no mention of whether the upper-lobe orifice or the lingular orifice was narrowed or not. At that time the lower-lobe bronchus showed

*Assistant in surgery, Massachusetts General Hospital.

an area of narrowing. There was a shadow in the left-lung field, and the problem is to reach a decision about what caused it. The first condition I should like to mention is carcinoma, which one must always consider in any unusual shadow in a lung field, especially in a patient of this age. However, this lesion had apparently been present for at least two and a half years, with little change. I think that is against carcinoma. There was also a negative bronchoscopy and negative cytologic study. Pain in the left chest would be unusual for a carcinoma of that duration that was not more extensive. Also, the patient had lost too much weight for the entire condition to be attributed to carcinoma.

Another condition that must be considered is chronic lung abscess. I think the fact that this lesion had remained fairly constant by x-ray study without ever showing any areas of mottling and also without showing a fluid level at any time on repeated examinations is against a chronic lung abscess. Also, the fact that little sputum was reported at any time is against it.

This lesion, of course, could have been bronchiectasis involving the lingula of the left upper lobe. What information is given indicates that there was no filling at the time of bronchography so that this was probably not due to bronchiectasis alone.

Of course, one must consider bronchial tuberculosis. Stenosis of the bronchi can occur with pulmonary tuberculosis and collapse at the periphery. I can assume that this patient had had tuberculosis in the past from the Ghon complex that Dr. Wyman has pointed out and also from the calcified lymph nodes seen in the region of the bronchus. A negative sputum and lack of change of the lesion are against this.

The fifth condition to consider is chronic pneumonitis, and I believe that is the diagnosis in this patient. There are a number of things in favor of it. In the first place there had been a definite history of pneumonia in the past, apparently a fairly typical left-lower-lobe pneumonia. The second thing in favor of the diagnosis was the collapse in this particular region, with little change over the two years, as shown in the x-ray films. A history of recurrent upper-respiratory-tract infection is frequent in cases of chronic pneumonitis. The fourth finding that goes with this is the dry cough, with only occasional raising of sputum. The fifth condition that is seen in many of these cases is constant or at least intermittent pain in the back. Pain has been a symptom of half the cases of chronic pneumonitis reported. Also, the tiredness, the considerable weight loss and slight dyspnea are all consistent with this diagnosis. From the history I think we can eliminate the possibility of lipoid pneumonitis.

Chronic pneumonitis has occurred without obstruction of the bronchus leading to the involved segment. Waddell, Sniffen and Sweet* reported 10 cases from this hospital, and in none of them were they able to demonstrate obstruction of the bronchus. Chronic pneumonitis usually follows a pneumonia. The reason for the development of chronic pneumonitis is not known. One theory is that the pneumonia sputum is so thick and viscid that it obstructs the small bronchioles and leads to chronic infection. Bronchial obstruction is also seen in the cases of chronic pneumonitis. Now the obstruction of the bronchus may be intrinsic or extrinsic because of inflammation of the peribronchial lymphatics or pressure from the lymph nodes. In the right lung a ring of lymph nodes around the middle-lobe bronchus is frequently seen. These nodes drain the lower lobe as well as the middle lobe and frequently become enlarged, with infection of either lobe. The lingular bronchus of the left upper lobe is the comparable bronchus on the left side, and frequently there are large nodes around it. The enlargement of these lymph nodes can occlude the bronchus and cause the development or persistence of pneumonitis beyond.

In this particular case there was a history of pneumonia in the left lower lobe, a history of recurrent infection in the lung and definite evidence that there had been in years gone by probably a tuberculous infection of the left lower lobe with inflammation and calcification of the hilar lymph nodes in that region. Therefore, my diagnoses are chronic nontuberculous pneumonitis of the lingular segment of the left upper lobe, a healed tuberculous focus in the left lower lobe, with hilar lymphadenopathy and calcification, and narrowing of the lingular bronchus by enlarged lymph nodes.

Dr. John Quinby: Does this chronic pneumonitis differ from bronchiectasis?

Dr. Gephart: Yes; it does. As I understand it the chronic pneumonitis starts out with a low-grade infection in a particular segment of the lung, with gradual scarring and replacement of the bronchial walls, and some fibrosis. Eventually, if these cases are allowed to go on long enough they will probably develop bronchiectasis, but it may take as long as twenty years to do it.

Dr. David Freiman: It may certainly take some time to develop bronchiectasis under these conditions. The bronchial dilatation apparently results from collapse of the segment, with increased tension on the diseased bronchi within the collapsed area as a result of the increasingly negative intrapleural pressure.

Dr. Gordon Scannell: This patient was explored by Dr. Edward D. Churchill after bronchoscopy just prior to operation. Our diagnosis before this procedure had been much as Dr. Gephart has

*Waddell, W. R., Sniffen, R. C., and Sweet, R. H. Chronic pneumonitis: its clinical and pathologic importance. *J. Thoracic Surg.* **18**:707-737, 1949.

described, but when at bronchoscopy a rather smooth endobronchial polypoid lesion was seen we settled upon adenoma as the most likely diagnosis. At thoracotomy the entire left upper lobe was reduced in volume, and although the apical posterior and anterior segments contained air, they did not expand or collapse normally. The lingular segments were also reduced in volume, and these did not contain air. A left upper lobectomy was carried out with relative ease although there were moderately vascular inflammatory changes in the region of the lingular bronchus, with several firm lymph nodes at the hilus.

Clinical Diagnosis

Adenoma, left-upper-lobe bronchus.

Dr. Gephart's Diagnoses

Chronic pneumonitis, lingular segment of left upper lobe.
Healed tuberculous focus, left lower lobe.
Hilar lymphadenopathy, with calcification leading to narrowing of bronchus and bronchiectasis of the lingular segment of left upper lobe.

Anatomical Diagnoses

Obstruction of main-stem bronchus to lingula (left upper lobe) by caseous focus, probably tuberculous.
Bronchiectasis, superior and inferior lingular segmental bronchi, severe.
Chronic pneumonitis, lingular segment.

Pathological Discussion

Dr. Freiman: The specimen received in the laboratory was the left upper lobe of the lung. The anterior and the apical posterior segments were crepitant and seemed entirely normal. The lingular segments, both the superior and inferior, were firm, and on section were replaced by dense fibrous tissue. The lingular bronchi were very much dilated and fusiform throughout, the bronchiectasis being most prominent in the inferior segment. Examination of the main-stem bronchus to the lingula just proximal to its division into superior and inferior branches revealed a firm, calcified nodule about 6 cm. in diameter that almost totally obstructed the lumen. On section this proved to be a focus of obsolete caseous material surrounded by dense fibrous tissue that involved the whole wall of the bronchus extending between the cartilage plates to the surrounding pulmonary parenchyma. Such lesions are usually interpreted as being tuberculous although other etiologic agents may cause the same type of reaction in the lung. In this case no evidence of tuberculous activity could be demonstrated histologically either in the bronchus, the lung or the one lymph node that was available for examination. The collapsed segments showed extensive chronic pneumonitis, chronic bronchitis and bronchiectasis.

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GLADLY LEARN AND GLADLY TEACH

The term nonteaching when applied to a hospital should mean only that the institution does not have a specific affiliation with any school of medicine. As Halsted brings out in his paper published elsewhere in this issue of the *Journal*, however, any hospital that pretends to do a complete job as such must have teaching as one of its important functions. The same qualification, indeed, may be applied to almost any of the professional, economic or industrial activities of man where precept and example may be found, or where it is necessary that personnel be trained.

Wherever two or three are gathered together, there the process of education may be taking place. A classic example of pure simplicity in education is Garfield's familiar log with Mark Hopkins sitting on the other end; for these two there was the very hub, for the moment, of teaching and of learning.

In Halsted's so-called nonteaching hospital, not only must opportunity be provided for resident training, but a teaching program must be planned for the practicing physician as well. Here is the material and here is the varied experience; from it educational advantages should be made available for all who participate — for intern and resident and visiting physician, for nurse and certainly for patient, not mentioned by Halsted except in regard to his improved care. Here too, as a fundamental spoke in the turning wheel of medicine, clinical investigation can and should be carried on. Details must be arranged and someone must be responsible for the over-all organization of the teaching program. It must be financed. It must have some symbiotic attachment to a university hospital whereby special knowledge and skills may be brought to the peripheral institution and whereby the specialist himself, God willing, may learn something from the general practitioner beyond his garden gate.

The school bell must ring each term for butcher and baker, for doctor and lawyer. He who does not constantly enrich his mind with new knowledge may find eventually that his capacity for forgetting will leave little of value behind. And no dog, however old, need ever say that he can learn no new tricks.

The doctor, wherever his path may lie, can still emulate to some degree Chaucer's clerk of Oxenford, for

"— gladly wolde he lerne, and gladly teche."

THE MOUNTAIN LABORS

The attitude of organized labor — organized, it is widely believed, for the benefit of labor — toward organized medicine, the intent of which is to provide the best possible medical service to the entire nation, may occasionally elicit mild surprise. One wonders why labor is so opposed to the efforts of the American Medical Association in maintaining a system of free enterprise in the practice of medicine in this country, and one might even be a little dis-

turbed at the heat that the editors of labor are capable of generating over the subject.

It can hardly be that medicine has always served the working man so ill as to deserve so much condemnation from his editorial spokesmen now, and one may question if there is not rather an ulterior motive being served than that the present attacks on American medicine arise from any deep-seated convictions of its sinfulness.

The news sheet *Labor*, on August 12, under the heading PROPAGANDA (*sic!*) prints "two stories which show to what lengths the 'Doctors' Trust' — the American Medical Association — has gone in spreading false propaganda about health insurance." The first of these deals with the attitude of the American Medical Association toward the British health program, and the second with a "revelation" by the Committee for the Nation's Health on the "staggering amount of propaganda" that is being put out by the "Doctors' Trust" and its allies.

The *League Reporter*, which is published weekly by Labor's League for Political Education of the American Federation of Labor, contains in two pages on August 7 no less than four items directed against the American Medical Association. "The American Medical Association," according to the Washington Column of the *League Reporter*, "has dropped all pretense at opposing national health insurance on a dignified, professional level. It now has become a huckster of propaganda."

Again on August 14 the *League Reporter* comments unfavorably on the opposition of the American Medical Association to the President's plan for national health insurance, and on September 4 proclaims a veritable hymn of hate that allegedly rises from the multiple throats of the American Medical Association, references not being given:

> The American Medical Association (AMA) says it hates any and all kinds of Government aid. It hates national health insurance. It hates free medical care for dependents of servicemen. It hates financial help for badly needed medical schools. It hates disability insurance.

The more one reads, however, the more one wonders if the animus may not be synthetic; the occasional froth a matter of soapsuds dramatically applied about the oral orifice; the fine fervor the result of an artificial flagellation of the editorial adrenal glands.

Is the American Medical Association being used, perhaps, as a whipping boy to serve some further political end? Otherwise it seems to be something of a stuffed mouse that labor's mountain has brought forth.

AND/OR

THE lexicographic successors of Noah Webster, entrusted with the responsibility of keeping up to date the classic that he originally produced, have conceded that "sometimes in legal papers *and/or* is used to represent *and* as interchangeable with *or*." To the legal usage a mathematical one might also be added, although it is not mentioned even in the New International edition of Mr. Webster's authoritative work. In writing that has any pretense to literary merit the appearance of this conjunctive Siamese twin, expressed in the form of an arithmetic fraction and pregnant with all the subtlety of a telegram, is almost more than the reader with ordinary literary appreciation should be expected to bear.

Unfortunately many amateur authors of today and not a few professionals inflict this verbal transgression on their readers not once but sometimes frequently on the same page, as if conscious of having fought a round with the English language and come up the winner. It is indeed a round won, in a way, amounting almost to a knockout except that the blow is foul. And certainly this particular part of speech is neither fish nor flesh.

And/or is a triumph of superfluous brevity, ingenious in its very awkwardness; clumsily clever in the way that it avoids the obvious, correct and clear "or both." The patient need not have pneumonia and/or typhoid fever. With far greater propriety he may have pneumonia or typhoid fever or (unfortunately) both.

Bad writing serves no useful purpose that cannot be served better by good writing; the continued appearance of the leap-frog conjunction can be attributed only to carelessness and/or ignorance.

ACCIDENT HANDBOOK

THE Boston Children's Hospital has issued a twelve-page pamphlet on durable paper, prepared by its staff and Public Relations Department, which should have an important place in every home. Eight important accidents happening in the home are discussed: head injuries, burns, poisons, cuts, fractures, bites, convulsions and foreign bodies. Tabs on the pages provide ready reference. On one page, under each heading, advice is given about *What Not to Do*, and on the opposite page *What to Do*, with interesting small illustrations on the pages.

As a further aid in preventing accidents to children in the home the booklet includes a safety check list, which warns about the principal hazards existing in the home.

The *Handbook*, which was prompted by the fact that many children came to the hospital because of accidents in the home, often improperly cared for, has been issued in an attempt to prevent some of these occurrences and to lessen the resulting disability. It is designed to be hung by the telephone, and provides space on the back cover for telephone numbers of physician, druggist, fire and police departments, hospitals and taxi service.

The first issue of 100,000 copies has been exhausted, and many orders are pouring in from individuals, institutions and firms for copies to distribute to employees, customers, families and so forth. A real forward movement in preventive medicine has been taken by the Hospital in issuing such a pamphlet, and many physicians will undoubtedly desire to commend the *Handbook* to their patients.

The following hit at the water cure was made by Charles Lamb, and no one but himself could have had so quaint a conceit: — "It is," said he, "neither new nor wonderful, for it is as old as the Deluge, which, in my opinion, killed more than it cured."

Boston M. & S. J., *November 6, 1850*

MASSACHUSETTS MEDICAL SOCIETY

PRACTITIONER OF THE YEAR

Dean Sherwood Luce, of Canton, was unanimously selected by the Executive Committee of the Massachusetts Medical Society, at a special meeting held on October 18, as the Society's candidate for the general-practitioner-of-the-year award of the American Medical Association.

Dr. Luce was born in Holliston seventy-four years ago, the son of a Yankee sea captain. A graduate of Harvard Medical School, he was admitted to fellowship in the Massachusetts Medical Society in 1908, since which time he has been engaged in the general practice of medicine in Canton. In addition to being the outstanding practitioner of Canton he has served on the Board of Health, and has been school physician and a trustee of the public library. He was a captain in the Medical Corps in World War I and served on the Selective Service Board of Canton in World War II.

To those who know him, either personally or by repute, Dr. Luce is a singularly fitting candidate for this honor.

DEATHS

BOWKER — John W. Bowker, M.D., of Somerset, died on August 11. He was in his seventy-seventh year.

Dr. Bowker received his degree from University of Vermont College of Medicine in 1900. He was a member of the staffs of Hamot and St. Vincent's hospitals.

His widow, a son, a daughter, and a brother survive.

GALLIGAN — Edward J. Galligan, M.D., of Taunton, died on September 25. He was in his eighty-second year.

Dr. Galligan received his degree from College of Physicians and Surgeons of Baltimore in 1896.

A son survives.

GRACE — James J. Grace, M.D., of Springfield, died on October 17. He was in his forty-fifth year.

Dr. Grace was a member of the staff of Mercy Maternity Hospital and was a school physician.

His widow, two sons and a daughter survive.

HARRISON — Columbus W. Harrison, M.D., of Boston, died on October 15. He was in his seventy-second year.

Dr. Harrison received his degree from Tufts College Medical School in 1906. He was a fellow of the American Medical Association.

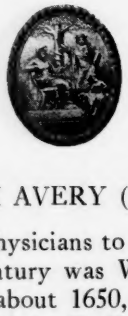
His widow, a son and a daughter survive.

STREET — Charles E. Street, M.D., of Springfield, died on October 14. He was in his seventy-eighth year.

Dr. Street received his degree from University of Michigan Medical School in 1902. He was a fellow of the American Medical Association.

A brother survives.

BOSTON MEDICAL LIBRARY



WILLIAM AVERY (1622-1686)

One of the first physicians to come to America in the seventeenth century was William Avery, who arrived in Boston about 1650, with his wife and children, and settled in Dedham. He served as a physician, although his educational qualifications in medicine are not known. Avery was also a "gentleman," with a coat of arms. He is buried in King's Chapel in Boston. He left, in his will, his "two stills, all my physick books and instruments," to his son.

Avery kept in touch with his friends at home, particularly Robert Boyle, on scientific matters, but his chief interest to us lies in his medical letters, a number of which have been preserved in the library of the Massachusetts Historical Society. Recently another has come to the Boston Medical Library. Written in 1663, it instructs the recipient, apparently a minister residing in another town, in the care of an ulcer, particularly in the making of an ointment to be used as a dressing.

CORRESPONDENCE

REVOCATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held September 21, 1950, it was voted to revoke the registration of Dr. Walter L. McClintock, of Quincy, because of ill health.

GEORGE L. SCHADT, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

BIOPSY OF LIVER

To the Editor: I read with interest the article by Gallison and Skinner entitled "Bile Peritonitis Complicating Needle Biopsy of the Liver" in the July 13 issue of the *Journal*. Since their report referred to work of our group (Kinsell, L. W., Weiss, H. A., Michaels, G. D., Shover, J. S., and Barton, H. C., Jr. Correlation of hepatic structure and function. *Am. J. Med.* **6**:292, 1949) I feel free to comment. The men who co-operated in the investigations at Oakland are now working in various institutions. Cumulatively, they have performed more than 500 biopsies of the liver without serious complications. This is considered to be due to good fortune, to careful selection of cases, to technic and, by no means of least importance, to the type of needle employed.

We selected the Vim–Silverman needle because it seemed to produce the least trauma. Needles of large caliber used for aspiration of tissue and those with serrated edges that cut out a piece of tissue seem to have the disadvantage of leaving a defect in the capsule of the liver. The Vim–Silverman needle, on the other hand, is of reasonably small diameter, and the cutting portion is introduced into the tissue beneath the capsule. When the section is obtained and the needle is withdrawn, a minimal defect is left in the capsule. This closes after the needle is removed. This has been observed through the peritoneoscope, which we used for visualization of the procedure in our early cases. The apparent disadvantage of this type of needle is the somewhat smaller portion of tissue obtained for study. However, the pathologists co-operating with us have been satisfied with the results.

It is urged that other investigators carefully consider the type of needle used in performing liver biopsies.

H. A. WEISS, Lieutenant Commander (M.C.),
United States Navy

United States Naval Hospital
San Diego 34, California

OCCURRENCE OF HERPES ZOSTER IN AUREOMYCIN THERAPY

To the Editor: Since September, 1949, an increasing number of articles reporting excellent clinical improvement with aureomycin in the treatment of herpes zoster have appeared. When administered early in the disease, this antibiotic apparently causes rapid healing of the herpetic lesions; when it is given late, the results are not as dramatic.

In an article entitled "New Antibiotics: Polymyxin, Chloromycetin, and Aureomycin" (*J. Mt. Sinai Hosp.* **16**: 71, 1949) Schoenbach reported the development of herpes zoster in 2 patients during the course of aureomycin treatment for other infections that occurred after nephrectomy.

In another closely related disease, herpes labialis, a similar situation has been reported. Finland and his associates, in a study on the subject "Aureomycin Treatment of Herpes Zoster" (*New Eng. J. Med.* **241**:1037, 1949), reported 4 cases in which herpes labialis occurred and extended during treatment with adequate doses of aureomycin given for bacterial infection.

In a case recently observed herpes zoster developed while the patient was receiving aureomycin for another infection. This fifty-two-year-old housewife was first seen because of a pulmonary infection, and a diagnosis of virus pneumonia of the right lower lobe was made. Aureomycin was given in dosage of 500 mg. every six hours for two days and reduced to 250 mg. every four hours for the next three days. During these three days she became afebrile, her condition greatly improved, and the drug was discontinued. Six days after aureomycin was first started, there was a recurrence of fever, cough, malaise and clinical evidence of pneumonia at the left-lung base, and lesions typical of herpes zoster were noted along the distribution of the right sciatica nerve. She had first noted these lesions two days before (the fifth and last day of drug therapy) but had thought they were merely a skin reaction to the medication. Because of the spread of the pneumonia, aureomycin was given again in dosage of 500 mg. every six hours. In two days she became afebrile and the dosage was decreased to 250 mg. every 4 hours for the next five days, at which time the pneumonia had rapidly resolved. However, the course of the herpes zoster did not appear to be altered. On examination four months later several of the encrusted lesions remained.

Typical herpes zoster appeared and progressed while this patient was receiving adequate dosage of aureomycin given for virus pneumonia; the disease (herpes zoster) was not altered by another course of therapy given for a spread of the pneumonia to the other lung.

From these observations and those reported by Schoenbach it may be concluded that herpes zoster may occur although aureomycin is given in adequate dosage for a simultaneous infection. As suggested by Finland and his associates, the lack of response in these cases of herpes zoster may be because there are strain differences in the susceptibility of the virus. Now that aureomycin is more extensively prescribed, more observations similar to the one presented will probably be seen, and the specific value of aureomycin in the treatment of this disease can be determined.

JOSEPH P. MCCRACKEN, M.D.

212 West Main Street
Durham, North Carolina

BOOK REVIEWS

Louis Pasteur: Free lance of science. By Rene J. Dubos, Ph.D. 8°, cloth, 418 pp., with 12 illustrations. Boston: Little, Brown and Company, 1950. $5.00.

When René Vallery-Radot published in 1922 his monumental *Life of Pasteur*, it immediately became the authentic, authoritative biography of the great French scientist, and is not likely to be supplanted. This new life of Pasteur by Professor Dubos, himself a scientist of great distinction, well known in Boston and present editor of the *Journal of Experimental Medicine*, does not aim to be a complete, chronologic, factual biography, but rather an appraisal and evaluation of Pasteur's contributions to science and society in terms of the problems that he successively undertook and solved. His greatness consists not merely in the facts that he solved these problems, demonstrated the scientific method and became the foremost scientist of the nineteenth century but also in the fact that he established permanently the pattern of research and of the scientific life.

Written with fascinating literary style and from personal experience and knowledge, this story of Pasteur's achievement, and of its far-reaching impact on civilization, is a memorable contribution to understanding of its significance and value. It is illustrated with 12 portrait plates, obtained through the assistance and courtesy of Professor Vallery-Radot, Pasteur's grandson, and of Doctor Henriette Noufflard.

Training for Childbirth: A program of natural childbirth with rooming-in. By Herbert Thoms, M.D. 8°, cloth, 114 pp., with illustrations. New York: McGraw-Hill Book Company, Incorporated, 1950. $3.00. (McGraw-Hill Series in Health Science.)

This intensely interesting monograph is a logical sequel of Grantly Read's *Natural Childbirth*. It presents an expanded program of physical and psychologic preparation for childbirth, designed by the distinguished Yale obstetrician and successfully employed by him in his own work during the past decade. Actually, it is very similar to methods practiced and taught at Harvard half a century ago, before the development of the later trend toward more frequent operative intervention and the regarding of labor as a purely suggical procedure in which the patient plays little or no conscious part. The author does not claim that "natural childbirth" eliminates surgery, but, in the series of 546 cases that he reports, it is noteworthy that the percentage of operative deliveries and of episiotomies is lower than is usual in similar statistical series nowadays.

This book has an admirable foreword by Dr. Amos Christie, consulting editor of the Health Science Series in which it is published, and is illustrated by 8 plate engravings and 8 line drawings. It should be thoughtfully read and taken to heart by every American obstetrician.

Practical Neurological Diagnosis: With special reference to the problems of neurosurgery. By R. Glen Spurling, M.D. Fourth edition. 8°, cloth, 268 pp., with 101 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $5.00.

In fifteen years this book has passed through four editions, an acknowledged tribute to its usefulness. The new printing has received some editorial revision, but many unclear statements remain. The book deals largely with conditions that are open to surgical treatment and misses much of medical neurology. Its chief weakness lies in its incompleteness.

The Pathology of Articular and Spinal Diseases. By Douglas H. Collins, O. B. E., M.D. (Liverp.). 8°, cloth, 331 pp., with 199 illustrations. Baltimore: Williams and Wilkins Company, 1950. $7.00.

Disorders of the skeletal systems are frequently neglected by general pathologists, partly because they are seldom fully investigated at autopsies and partly because of the difficult histologic technic needed to disclose the lesions for complete evaluation. Scant reference to bone and joint disease is usually afforded in textbooks on pathology, and the orthopedist and radiologist do not have much better sources of reference. The author, long a student of rheumatism and allied diseases, has admirably filled the gap. His book is orderly, well written and finely illustrated. As an objective record of the pathology of bone disease, it is outstanding. Theories of causation with note of adrenal, hyperparathyroid and pituitary syndromes, are briefly considered in an adequate manner, but the chief emphasis is on pathology. Documented and indexed, the book is impressive as a fundamental text. Particular attention should be called to the fine printing, clear illustrations and general pleasing appearance of this important addition to the medical literature.

Harvey Cushing: Surgeon, author, artist. By Elizabeth H. Thomson. With a foreword by John F. Fulton, M.D. 8°, cloth, 347 pp., with 12 plates. New York: Henry Schuman, 1950. $4.00.

Harvey Cushing was such a complex character that many facets were not fully explored by John F. Fulton in his official "Life," published in 1946. Miss Thomson has picked up a number of the missing sidelights, pouring over the memorabilia, scrapbooks, notebooks, diaries, correspondence files, annual reports of Cushing's Hospital, kept so meticulously from 1914 to 1933 during his most productive years, and the articles on him, published since 1946, including the book reviews. Cushing seems to have kept "everything," presumably in preparation for an autobiography, but there is still much ground to be explored. Miss Thomson's book is pleasing, light and comprehensive, without being detailed, emphasizing the family life of the Cushing household, particularly the considerable influence of Mrs. Cushing, and giving a satisfactory picture of a man of genius, whose impact on medicine will long be felt. The part Fulton played in Cushing's life is well brought out, something that could not be emphasized in Fulton's work. It is hoped, however, that everyone reading this biography will be led to Fulton's splendid biography for reading or re-reading.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Biochemistry of the Teeth. By Henry M. Leicester, Ph.D., professor of biochemistry, College of Physicians and Surgeons of San Francisco, School of Dentistry. 8°, cloth, 306 pp., with 5 illustrations. St. Louis: C. V. Mosby Company, 1949. $5.00.

This monograph on an unusual subject discusses the chemical composition, physical properties and formation of teeth, mineral metabolism and the teeth, the effect of vitamins, hormones and other substances on the development of teeth, and dental caries. The literature on the subject is extensively surveyed, and long lists of references are appended to the various chapters. There are author and subject indexes. The type is large, and the printing well done on a soft, nonglare paper. The book is recommended as a reference text for all medical and dental libraries.

Haemolytic Disease of the Newborn. By M. M. Pickles, D.M., Nuffield Graduate Assistant in Clinical Pathology, Radcliffe Infirmary, Oxford. 8°, cloth, 181 pp., with 21 illustrations and 19 tables. Springfield, Illinois: Charles C Thomas, 1949. $4.50.

This special monograph is based on a five-year study of 73 families and 116 affected children. The material is well organized, and after a short chapter on the history of the disease, there are chapters on the Rh antigens and antibodies and their relation to hemolytic disease; the pattern of the disease, divided into two classes (hydrops fetalis and macerated fetus and icterus gravis and anemia neonatorum), treatment; and sequelae. Appended to the text are an extensive bibliography and author and subject indexes. The publishing is excellent; the printing was done in Great Britain.

The Salt-Free Diet Cook Book. By Emil G. Conason, M.D., and Ella Metz. 8°, cloth, 144 pp. New York: Lear Publishers, Incorporated, 1949. $3.00.

This diet book should prove useful to physicians and others interested in the salt-free and low-sodium diets.

Progress in Biochemistry: A report on biochemical problems and on biochemical research since 1939. By Felix Haurowitz, M.D. (Prague), D.Sc. (Prague), professor of chemistry, Indiana University, Bloomington, Indiana. 8°, cloth, 405 pp., with 7 illustrations. New York: Interscience Publishers, Incorporated, 1950. $7.50.

This progress report is an essential reference work for the biochemist and for medical libraries. The field of biochemistry is well covered in twenty-four chapters. Extensive bibliographies are appended to the various chapters, and there is a good index. The text was written in 1948. The printing was done in Switzerland; the publishing is excellent.

NOTICES

ANNOUNCEMENTS

Dr. Basil C. Gray announces the opening of an office for the practice of dermatology at 572 Washington Street, Wellesley, in addition to his present office at 416 Marlboro Street, Boston.

Dr. Norman A. Harvey announces the opening of his office at 4 Ackley Street, Glens Falls, New York, for the practice of pediatrics.

Dr. Katharine Kiehl announces the opening of an office for the practice of pediatrics at 639 Washington Street, East Walpole.

Dr. Richard J. LaVigne announces the opening of an office for the practice of radiology at the Burbank Hospital, Fitchburg.

ST. ELIZABETH'S HOSPITAL

A clinical meeting of the staff of St. Elizabeth's Hospital, Brighton, will be held on November 10 at 12 noon.

PROGRAM

Ocular Manifestations of Migrainoid Headaches. Hugh C. Donahue, M.D.
Ocular Manifestations of Certain Degenerative Diseases. Thomas Cronin, M.D.
Ocular Manifestations of Certain Skin Disorders. Thomas White, M.D.

All interested physicians are cordially invited to attend.

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of the Peter Bent Brigham Hospital, Boston, on Tuesday, November 14, at 8 p.m., with Dr. G. W. Thorn presiding.

PROGRAM

Radiologic Aspects of Vitamin D Intoxication. Dr. Merrill C. Sosman.
The Effect of ACTH on Tuberculin Allergy. Drs. Charles Osgood and C. B. Favour.
Tagging of Red Cells and Proteins with Radioactive Chromium. Drs. Seymour J. Gray and Kenneth Sterling.
An Analysis of Components in the Metabolic Response to Surgery. Dr. Francis D. Moore and Margaret R. Ball.
A Reproducible Controlled Unilateral Lower-Nephron Nephrosis in Dogs. Drs. Chester B. Rosoff, Andrew C. Jessimin, Robert S. Weiner and Carl W. Walter.
Studies in the Kinetics of Water Distribution in the Human Body. Drs. Isidore S. Edelman, John M. Olney, Paul R. Schloerb and Francis D. Moore.
Some Aspects of Abnormal Potassium Metabolism. Drs. John P. Merrill and Harold Levine.

SOCIETY MEETINGS AND CONFERENCES

NOVEMBER 1–29. Springfield Hospital. Page 679, issue of October 26.
NOVEMBER 10. American Trudeau Society. Page 280, issue of August 17.
NOVEMBER 10. St. Elizabeth's Hospital. Notice above.
NOVEMBER 13 AND 14. New England Diabetes Association. Page 721, issue of November 2.
NOVEMBER 14. Springfield Academy of Medicine. Page 722, issue of November 2.
NOVEMBER 14. New England Society of Anesthesiologists. Page 512, issue of September 28.
NOVEMBER 14. Harvard Medical Society. Notice above.
NOVEMBER 15. Massachusetts Society of Examining Physicians. Page 679, issue of October 26.
NOVEMBER 17. Society of American Bacteriologists, Northeast Branch. Page 722, issue of November 2.
NOVEMBER 20. Hartford Medical Society. Page 680, issue of October 26.
NOVEMBER 21. South End Medical Club. Page 721, issue of November 2.
NOVEMBER 27–JUNE 4. New England Cardiovascular Society. Page 680, issue of October 26.
NOVEMBER 27. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.
NOVEMBER 28. Norfolk District Medical Society. Page 629, issue of October 19.
DECEMBER 4. Hartford Medical Society. Page 680, issue of October 26.
DECEMBER 7–9. New York State Society of Anesthesiologists. Page 582, issue of October 12.
DECEMBER 9. American Federation for Clinical Research. Page 680, issue of October 26.
DECEMBER 14. Treatment of Hyperthyroidism, Especially with Radioactive Iodine. Dr. Earle Chapman. Pentucket Association of Physicians. 8:30 p.m. Haverhill.
DECEMBER 18. Hartford Medical Society. Page 680, issue of October 26.
JANUARY 3. Hampshire District Medical Society. Page 170, issue of July 27.
JANUARY 22. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.
JANUARY 23. Norfolk District Medical Society. Page 629, issue of October 19.
JANUARY 31. American Academy of Orthopaedic Surgery (see Kappa Delta Award for Research in Orthopedic Surgery). Page 736, issue of May 4.
FEBRUARY 13. New England Society of Anesthesiologists. Page 512, issue of September 28.
FEBRUARY 27. Norfolk District Medical Society. Page 629, issue of October 19.
MARCH 26. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.
MARCH 27. Norfolk District Medical Society. Page 629, issue of October 19.
APRIL 9–13. American College of Physicians. Page 296, issue of June 15.
APRIL 10. New England Society of Anesthesiologists. Page 512, issue of September 28.
APRIL 24. Norfolk District Medical Society. Page 629, issue of October 19.
MAY 8. New England Society of Anesthesiologists. Page 512, issue of September 28.
MAY 9. Norfolk District Medical Society. Page 629, issue of October 19.
MAY 22–24. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.
MAY 24–26. American Goiter Association. Columbus, Ohio.
NOVEMBER 10–21, 1951. Pan-Pacific Surgical Association. Page 680, issue of October 26.

DISTRICT MEDICAL SOCIETIES

HAMPSHIRE

JANUARY 3. 4:30 p.m. Veterans Administration Hospital, Northampton.
MARCH 7. 4:30 p.m. Cooley-Dickinson Hospital, Northampton.
MAY 2. 4:30 p.m. Annual Meeting. Jones Library, Amherst.

NORFOLK

NOVEMBER 28.
JANUARY 23.
FEBRUARY 27.
MARCH 27.
APRIL 24.
MAY 9. Annual Dinner.

All meetings except the Annual Dinner will be held at the Boston Medical Library, 8 Fenway, at 8:00 p.m.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 16

THURSDAY, NOVEMBER 16
*9:00–11:00 a.m. Medical Grand Rounds. Joseph H. Pratt Diagnostic Hospital.

FRIDAY, NOVEMBER 17
*9:00–10.00 a.m. Medical Conference. Joseph H. Pratt Diagnostic Hospital.
*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*10.00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street, Boston.
*1:30 p.m. Tumor Clinic. Out-Patient Department, Mount Auburn Hospital, Cambridge.

(Notices concluded on page xv)

NOTICES (*Concluded from page 762*)

SATURDAY, NOVEMBER 18

*9:00–10:00 a.m. Surgical Grand Rounds. Joseph H. Pratt Diagnostic Hospital.

MONDAY, NOVEMBER 20

*11:30 a.m.–12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

TUESDAY, NOVEMBER 21

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

WEDNESDAY, NOVEMBER 22

*12:00 m. Clinical Discussion. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.

*12:00 m.–1:00 p.m. Clinicopathological Conference. (Children's Medical Center.) Amphitheater, Peter Bent Brigham Hospital.

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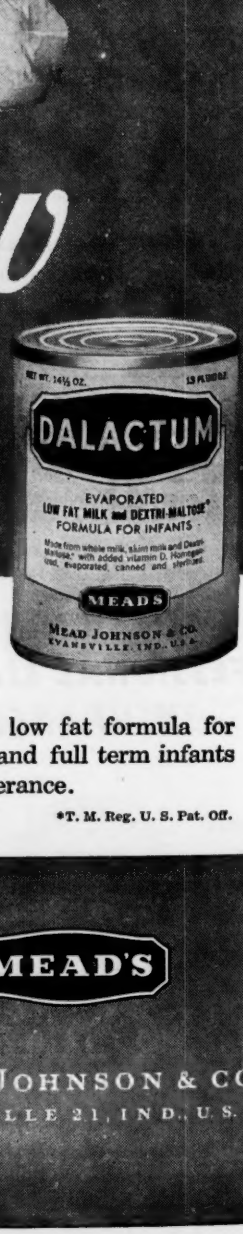

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